Under pressure

Vulnerability and stress in recurrent depression and new technologies to prevent relapse

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Table of Contents

Chapter 1

General introduction

According to the Global Burden of Disease study (GBD, 2010), the highest proportion of the total burden of all mental and substance use disorders is caused by Major Depressive Disorder (MDD) (Ferrari et al., 2013; Whiteford et al., 2013). In addition, MDD increases the risk of suicide and ischemic heart disease (Ferrari et al., 2013) and is linked to the development of somatic illnesses, such as diabetes (Monroe & Harkness, 2011). The risk of suicide in a depressed population is 20 times higher than in a non-depressed population (Holma et al., 2010). Depression is a highly recurrent disease and to reduce the burden of depression, we have to reduce the risk of recurrences and relapses.

Major Depressive Disorder

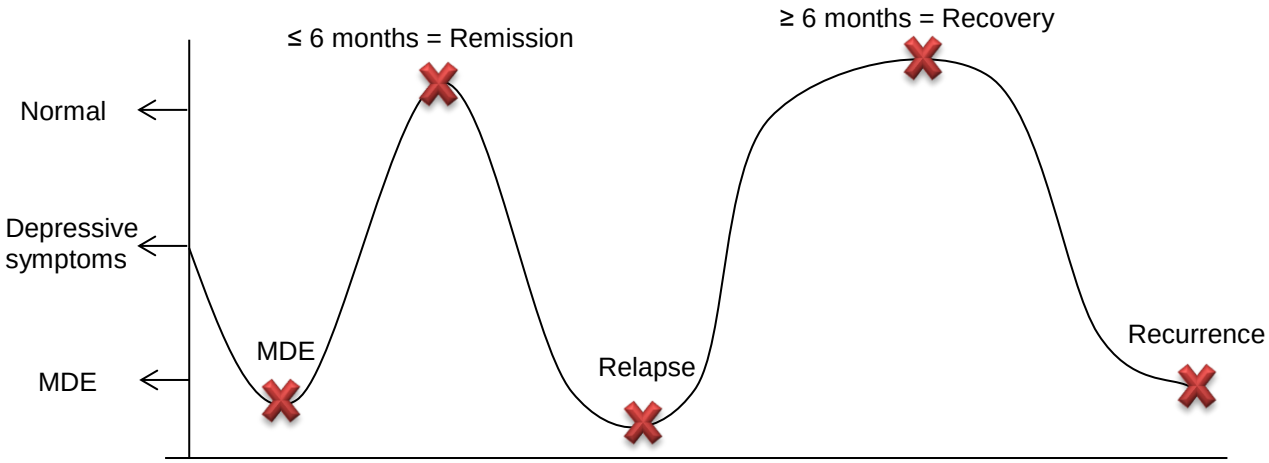
The diagnosis MDD is based on the simultaneous presence of minimally five symptoms for at least two weeks. One symptom has to be either a depressed mood and/or loss of interest and pleasure (symptoms presented in box 1). These key symptoms and at least three or four other symptoms have to be present almost every day, most of the day, for at least two weeks and are a distinct change to normal functioning. The symptoms lead to impairments in multiple domains such as family, social life and work (American Psychiatric Association, 2000). In the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V, published in 2013), MDD is defined by the same diagnostic criteria.

Box 1. DSM-IV-TR criteria Major Depressive Disorder (APA, 2010)

- Depressed mood most of the day.
- Diminished interest or pleasure in all or most activities.
- Significant unintentional weight loss or gain.
- Insomnia or sleeping too much.
- Agitation or psychomotor retardation noticed by others.
- Fatigue or loss of energy.
- Feelings of worthlessness or excessive guilt.
- Diminished ability to think or concentrate, or indecisiveness.
- Recurrent thoughts of death.

To describe the course of depression and interpret treatment outcomes, the operational criteria of Frank et al (1991) is often cited. According to these criteria, remission refers to the depression-free period of at least two months, and relapse refers to the onset of depression during the remission period. Recovery is considered once remission exceeds six months without relapse, and recurrence refers to the onset of depression after recovery (Figure 1). However, the terms relapse and recurrence are often used interchangeably and differentiating between them is not always possible (Beshai, Dobson, Bockting, & Quigley, 2011). For readability throughout this thesis, we refer to the more conservative term relapse in the case of both relapse and recurrence (Hollon, Stewart, & Strunk, 2006).

Figure 1. Phases of depression, based on the operational criteria of Frank et al. (1991)



Note, MDE=Major Depressive Episode

Recurrent depression

MDD is a chronic and lifelong disease (D. Richards, 2011), characterized by a dynamic course (Judd et al., 1998), and a high risk of relapse (Burcusa & Iacono, 2007). A long-term follow-up study in the general population demonstrated 15% of all patients to be unrecovered after 20 years and 38% of all patients to have relapsed after ten years (Eaton et al., 2008). This means that 53% did not recover at all, or had at least one relapse. The Netherlands Mental Health Survey and Incidence Study (NEMESIS), performed in the general population, showed similar percentages (Spijker et al., 2004). The National Institute of Mental health Collaborative Study of the Psychobiology of Depression (NIMH) demonstrated the probability of relapse to be 67% after 10 years (Keller & Lavori, 1984; Solomon et al., 2000), and 85% after 15 years (Mueller et al., 1999). Other clinic based studies present relapse rates ranging from 26.8%-33.5% over two years and 40%-60% over five years (Kanai et al., 2003; Kiloh, Andrews, & Neilson, 1988; Lee & Murray, 1988; Mattinson, Bogren, Horstmann, Munk-Jörgensen, & Nettelbladt, 2007; Surtees & Barkley, 1994). Furthermore, no significant differences between relapse rates in primary care and specialized mental health care were found (Hardeveld, Spijker, De Graaf, Nolen, & Beekman, 2013).

All these percentages demonstrate that there are patients who do recover and patients who do not recover. Estimates suggest that around 40-50% of all patients

will remain depression-free (Eaton et al., 2008; Lee & Murray, 1988; Monroe & Harkness, 2011). Therefore, Monroe and Harkness (2012), proposed that depression is both an acute mental disorder, as well as a life-long relapsing mental disorder. Both aspects have their own treatment needs and risk factors, and causes of depressive relapse might differ from causes of first onset of depression (Lewinsohn, Allen, Seeley, & Gotlib, 1999). Further, because of the depression-free periods in between episodes, recurrent MDD might be perceived as a distinct category of depression as well (e.g. Akkerhuis, Kupka, Groenestijn, & Nolen, 1996; Hollon et al., 2006). This is underscored by the specific risk factors associated with recurrent MDD, such as heritability (Pettit, Hartley, Lewinsohn, Seeley, & Klein, 2013).

Part I

Pathways to depressive relapse

Multiple risk factors are associated with depression onset such as, the presence of a somatic illness, a genetic predisposition, being female, presence of other psychopathology, personality traits such as high levels of neuroticism, a family history of depression, a history of adverse childhood experiences and stressful life events (for an overview: Belmaker & Agam, 2008; Burcusa & Iacono, 2007). With regard to relapse, well-known risk factors are a) prior episodes of depression, b) the presence of residual symptoms, c) genetics, d) age at first depression onset, e) severity of index episode, f) presence of comorbid axis I psychopathology, g) family history of psychopathology (especially depression or other affective disorders), h) stressful life events, i) dysfunctional cognitions, j) high neuroticism and k) poor social support (American Psychiatric Association, 2000; Bockting et al., 2005; Burcusa & Iacono, 2007; G. A. Fava et al., 2004; Judd et al., 1998; Mueller et al., 1999; Solomon et al., 2000; ten Doesschate, Bockting, Koeter, & Schene, 2010). However, for some factors that are associated with depression onset, the association with relapse is less well studied (chronic somatic illnesses), or the way these factors may cause relapse is unknown (childhood adversity, personality disorder).

Premorbid vulnerability

Based on a large-scale twin study conducted by Kendler et al. (2011), certain individuals have an early predisposition to a poor course of depression. This means that a vulnerability to recurrent depression is present even before the first onset of depression and relapse might be an inevitable consequence of premorbid vulnerability[1]. Based on the above mentioned risk factors, premorbid vulnerabilities might be heritable personality traits (such as neuroticism), family psychopathology and an early adverse environment.

An explanation for the influence of premorbid vulnerabilities on the depression course might be found in vulnerability-stress models (Abramson, Metalsky, & Alloy, 1989; Bleuler, 1963; Rosenthal, 1963; Zubin & Spring, 1977). According to these models, vulnerabilities are relatively stable aspects of a person, such as genes, that predispose someone to develop psychopathology after life stress. It is possible that premorbid vulnerabilities cause heightened life stress sensitivity on the long-term, irrespective of the number of previous episodes. Therefore, in people with premorbid factors, prevention of relapse treatment might be especially important. While we focus on life stress in this thesis, premorbid vulnerability could also influence other risk factors of depressive relapse, such as neuroticism and negative information processing (Burcusa & Iacono, 2007; Eaton, 2002).

Scarring

According to Post, Rubinow and Ballenger (1986), after several depressive episodes the recurrence of an episode will occur more autonomously: “The illness appears to evolve with its own rhythmicity and spontaneity, independent of life events” (pp. 191). This statement implies that the influence of, for instance, stress and vulnerability on the course of depression will diminish in the long term. The threshold to relapse is suggested to lower after multiple depressive episodes. In time, minor stress instead of major stress can already trigger a new episode (Mazure, 1998; Post & Weiss, 1998). This fits the classic and often cited example by Kraeplin

[1] In this thesis we define premorbid vulnerabilities as factors that were present before the first onset of depression.

(1921), of a women first becoming depressed after the death of her husband, next of her dog and then her dove.

An explanation for this process may be found in the scar hypothesis, in which episodes of depression leave scars that persist after remission and increase the vulnerability to depressive relapse in the psychological, social, and biological domain (Lewinsohn, Steinmetz, Larson, & Franklin, 1981; Oldehinkel, van den Berg, Bouhuys, & Ormel, 2003; Post, 1992). The increased vulnerability caused by scarring might lead to the return of episodes, thereby increasing vulnerability even more. This might explain why the number of depressive episodes is such an important predictor of depressive relapse.

Scarring refers to postmorbid (after an episode) vulnerability that was not premorbidly present (Ormel, Oldehinkel, & Vollebergh, 2004). Scars could, for example, alter personality in ways that increase susceptibility to stress and relapse (Hirschfeld & Klerman, 1979; D. N. Klein, Durbin, Shankman, & Santiago, 2002; Ormel, Oldehinkel, & Brilman, 2001). However, premorbid vulnerabilities might also be involved in this process and postmorbid vulnerability could be a continuation of premorbid vulnerability. Long-term follow-up of patients with assessment of potential premorbid vulnerabilities before their first onset of depression would be necessary to examine these hypotheses. Studies such as the Netherlands Study of Depression and Anxiety study (NESDA) might help answering these questions in the future. For now, in this thesis we focus on examining patients that have already experienced several previous episodes of depression to identify which factors impact the return of depression. Risk factors of relapse might act as moderators in the prevention of relapse and examining these factors might bring us a step closer in understanding, and possibly influencing, the pathways to depressive relapse.

Life stress

While major life stress, such as the death of a loved one, often precedes depression onset (Hammen, 2005), research demonstrates that minor life stress, such as waiting for a long time at an appointment, is an important predictor of depressive relapse (Bockting et al., 2006; Lenze, Cyranowski, Thompson, Anderson, & Frank, 2008; Monroe, Roberts, Kupfer, & Frank, 1996; Monroe et al., 2006; Ormel et al., 2001; ten Doesschate et al., 2010). While major life stress might still trigger a new episode of depression, after a certain number of episodes the impact on new

episodes seems to decrease (Monroe, Slavich, Torres, & Gotlib, 2007b). Less studied than major and minor life stress, is chronic life stress. With chronic life stress we refer to ongoing difficulties, for example difficulties that last at least six months or two years (T. A. Brown & Rosellini, 2011; Monroe, Slavich, Torres, & Gotlib, 2007a). An example of chronic life stress is having ongoing relationship difficulties or the presence of an illness. Chronic life stress is associated with the onset of depression (G. W. Brown & Harris, 1978), and is suggested to have an influence on recurrent depression as well. Research demonstrated major chronic life stress to be associated with a higher number of prior episodes of depression, while acute life stress was more often associated with a first onset depression (Monroe, Slavich, Torres, & Gotlib, 2007a). In this thesis we focus on minor and chronic life stress to examine whether they serve as triggers for depression after previous episode(s) or whether new episodes can occur independently of these stressors.

In the following section, the background and specific research questions with regard to the premorbid vulnerability, stress and cognitive vulnerability factors that were studied will be described.

Chapters in part I

Chapter 2: childhood adversity and minor stress sensitivity

A well-known premorbid vulnerability to depression onset is childhood adversity. Research shows that childhood adversity is often associated with a poorer course of depression, in terms of higher relapse rates and more persistent depression (Nanni, Uher, & Danese, 2012). An association with recurrent depression might be caused by the long-term heightened sensitivity to life stress resulting from childhood adversity (Comijs et al., 2007; Glaser, van Os, Portegijs, & Myin-Germeys, 2006; Tyrka, Price, Marsit, Walters, & Carpenter, 2012; Wichers et al., 2009, Nanni, Uher, & Danese, 2012). Conversely, in the ‘mismatch hypothesis’ early stressful life experiences are said to lead to better adaptability to later life stress (Frankenhuis & Del Giudice, 2012; Nederhof & Schmidt, 2012).

So far, two studies demonstrated that the experience of childhood adversity led to higher sensitivity to major or minor life stress, which successively heightened the risk of depression onset in adulthood (LaNoue, Graeber, de Hernandez, Warner, &

Helitzer, 2012; McLaughlin, Conron, Koenen, & Gilman, 2010). In contrast, a third study found that childhood adversity did not lead to an increased sensitivity to adult life stress in a cohort of 1887 older participants (Comijs et al., 2007).

However, depression might lead to life stress sensitivity as well which, in turn, heightens the risk for depressive relapse. Therefore, it is unknown whether the premorbid vulnerability childhood adversity, influences minor life stress sensitivity, and depression after multiple episodes. In chapter two, we examine the associations between childhood adversity, minor life stress and the return of depressive symptoms after remission in recurrently depressed patients, while controlling for the history of depression. If childhood adversity is an important predictor of minor life stress and depression, even after previous episodes, then this might indicate that premorbid risk factors indeed can influence the likelihood of yet another episode.

Chapter 3 and 4: presence of chronic somatic illness

Presence of a chronic somatic illness is considered to be an ongoing life stressor, predisposing someone to a poor depression course (American Psychiatric Association, 2010). In a review by Evans and colleagues (2005), depression was associated with a poor prognosis of multiple chronic somatic illnesses, such as cardiac disease, diabetes and cancer. Therefore, leading international practice guidelines for the treatment of MDD (American Psychiatric Association, 2010; National Institute for Health & Care Excellence, 2010; National Institute for Health and Care Excellence, 2009), advise longer maintenance treatment for depressed patients with comorbid chronic somatic illnesses.

Depression prevalence rates of individuals with a chronic somatic illness are two to three times higher than the prevalence rates of individuals without chronic somatic illnesses (American Psychiatric Association, 2010; Egede, 2007; Moussavi et al., 2007). Proposed mechanisms for this association are: genetics, life style, physiological disruptions due to over activation of the Hypothalamic–Pituitary–Adrenal (HPA) axis or the immune system (Egede, 2007; Katon & Schulberg, 1992; Licht et al., 2008; Moussavi et al., 2007; Penninx & van Dyck, 2010; Plotsky, Owens, & Nemeroff, 1998). Chronic somatic illnesses that are often associated with depression are heart diseases, obstructive lung diseases, diabetes, hypertension, human immunodeficiency virus, cancer and rheumatoid arthritis (American

Psychiatric Association, 2010; Iosifescu et al., 2003; Koike, Unützer, & Wells, 2002; National Institute for Health and Care Excellence, 2009).

Remarkably, no meta-analyses or systematic reviews described the risk of relapse in patients with versus without a chronic somatic illness. Therefore, we examined whether chronic somatic illness indeed is associated with a poor longitudinal course of depression, as described by the practice guidelines for treatment of MDD. In chapters three and four, a systematic review and a systematic review including a meta-analysis on the association between a chronic somatic illness and a poorer depressive course in terms of relapse and remission, are presented.

Chapter 5: personality disorder and cognitive vulnerability

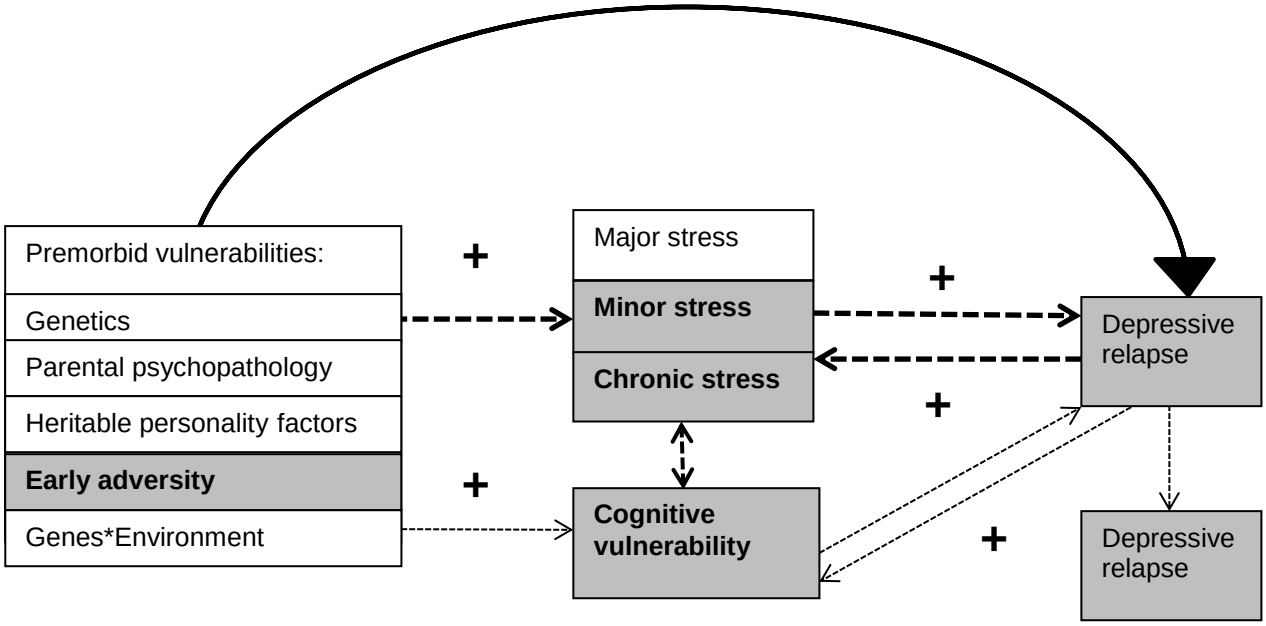
The presence of personality disorder is associated with a longer time to remission and an increased risk of depressive relapse (Grilo et al., 2010; Newton-Howes, Tyrer, & Johnson, 2006; Skodol et al., 2011). Personality disorder is perceived as a chronic life stressor activating cognitive vulnerability. As a first step in examining why a comorbid personality disorder might be associated with a poor depression course, in chapter five the association between personality disorder and cognitive vulnerability in remitted recurrently depressed patients is examined.

The prevalence of personality disorder in depression is high, even during remission (48%-51.9%), which might influence the risk of depressive relapse. (e.g. Farabaugh et al., 2007; Grilo et al., 2010; Pilkonis & Frank, 1988; Sato, Sakado, Sato, & Morikawa, 1994; Skodol et al., 2011). Cognitive vulnerabilities are potentially modifiable and might be an important treatment aim in patients with depression and personality psychopathology. Cognitive vulnerability was operationalized as cognitive reactivity and extremity, dysfunctional beliefs, and rumination. The relationship with stress was not examined in this chapter, but might be a next step in unraveling the relation between personality disorder and depressive relapse.

Research model Part I

In Figure 2 a model of depressive relapse is proposed. The premorbid vulnerability factors were selected out of the extensive review of Burcusa and Iacono (2007). Premorbid vulnerability might cause depressive relapse directly or indirectly via cognitive vulnerability or stress. An important factor in this model is depressive relapse itself, which might heighten stress sensitivity and cognitive vulnerability and may cause future relapse irrespective of environmental stress. The bold arrows and factors in grey boxes in Figure 2 are the focus of the current thesis. With regard to predicting depressive relapse, we focus on stress instead of cognitive vulnerabilities. However, we did examine the association between the chronic life stressor personality disorder and cognitive vulnerability. In addition, we examined the premorbid vulnerability childhood adversity, without considering other premorbid factors that may play an interactive or overlapping role, such as genes (Pettit et al., 2013). It is important to note that this model is not complete and offers a simplified representation of all the possible factors that influence the onset and return of depression, such as social support (Burcusa & Iacono, 2007).

Figure 2. Proposed research model of depressive relapse



Part II

Treatment of recurrent depression

As mentioned before, the risk of relapse increases with every other episode (American Psychiatric Association, 2000; Keller & Boland, 1998; Solomon et al., 2000), which stresses the importance of prevention of relapse. Various meta-analyses found acute phase psychotherapies to have a prophylactic effect (Beshai et al., 2011; Cuijpers et al., 2013; Vittengl, Clark, Dunn, & Jarrett, 2007). However, after acute phase treatment, when individuals do not meet the DSM-IV criteria for depression anymore, there still is a high proportion of patients who experience a relapse. Therefore, offering continuation therapy is recommended.

Continuation therapy is mostly similar to acute phase treatment; although the dose and frequency of Antidepressant Medication treatment (ADM) and psychological treatments, such as Cognitive (Behavioral) Therapy C(B)T, can differ (American Psychiatric Association, 2010). According to Guidi et al (2011), the treatment strategy should vary depending on “the nature, characteristics, and intensity of residual symptoms”. In line with this, C(B)T offered sequentially after ADM, or in combination with ADM, was associated with better long-term outcomes than ADM alone (Guidi et al., 2011). An extensive meta-analysis by Vittengl (2007), demonstrated a 61% likelihood of better outcomes for those treated with a combination of ADM and CT. The addition of C(B)T to ADM treatment reduced the risk of relapse with 23%. While C(B)T is more expensive in reaching remission than ADM, it has effects that last longer than ADM, making it a more effective treatment over time (Hollon, 2011). As an explanation, Guidi et al. (2011) mention that psychotherapies such as C(B)T teaches patients skills that remain effective even after treatment completion. These skills help to manage affective states and reduce the risks for relapse.

Research demonstrated that psychotherapies specifically focused on relapse prevention offered during (partial) remission to be effective as well in reducing the risk of depressive relapse (Guidi et al., 2011; Piet & Hougaard, 2011; Vittengl et al., 2007). Preventive psychotherapies are mostly based on C(B)T, but add strategies such as modifying dysfunctional attitudes in Preventive Cognitive Therapy (PT),

meditation in Mindfulness based CBT (MBCT) and improving well-being and balance in Well-being CT (Bockting et al., 2005; Bockting, Spinhoven, Wouters, Koeter, & Schene, 2009; G. A. Fava, Grandi, Zielezny, Canestrari, & Morphy, 1994; G. A. Fava, Grandi, Zielezny, Rafanelli, & Canestrari, 1996; G. A. Fava, Rafanelli, Cazzaro, Conti, & Grandi, 1998; G. A. Fava, Rafanelli, Grandi, Canestrari, & Morphy, 1998; G. A. Fava et al., 2004; Ma & Teasdale, 2004; Segal et al., 2010; Teasdale et al., 2000). Mostly, Preventive CT, Preventive CBT and MBCT were effective in patients with a higher number of previous episodes (Bockting et al., 2005; Ma & Teasdale, 2004; Stangier et al., 2013; Teasdale et al., 2000). Although some studies suggest that also patients with fewer episodes profit from these interventions (Geschwind, Peeters, Huibers, van Os, & Wichers, 2012). It has been suggested that these treatments work by disrupting internal depressive associations that develop during the course of depression (Beshai et al., 2011).

Internet-based treatments

Each episode of depression leads to considerable economic costs to society due to productivity losses and costs associated with health care uptake and also adds to emotional costs in individuals and their social networks (Johnson, Weissman, & Klerman, 1992; Keller & Boland, 1998; D. Richards, 2011; Smit, 2009). Prevention of relapse is therefore of great importance. Patients at high risk of relapse are said to require ongoing monitoring and treatment, specifically when prior episodes and residual symptoms are present (American Psychiatric Association, 2010; Andrews, 2001; National Institute for Health & Care Excellence, 2010). However, waiting lists due to scarcity of therapists are common (Cameron & Thompson, 2005), and therefore, in the past decade, less intense forms of psychotherapies, including Internet-based therapies (e-health) were developed and evaluated. According to National Institute for Health and Care Excellence (NICE) practice guidelines (2010), low intensity psychosocial interventions could be part of a stepped care approach. A stepped care approach may be a good fit for a disease characterized by fluctuations over time (Judd et al., 1998), where care is not always necessary but continued monitoring is warranted. Internet-based C(B)T is easily accessible and therapist involvement may be reduced, as demonstrated in acute phase Internet-based treatment (Wright et al., 2005).

In addition, monitoring by text messages makes it easier for the patient and therapist to detect relapse as early as possible, which might lead to a reduction in the burden of depression. Meta-analyses demonstrated small to moderate effect sizes of Internet-based therapies in the acute phase of depression, anxiety, panic disorders and alcohol use disorders (Andersson & Cuijpers, 2009; Barak, Hen, Boniel-Nissim, & Shapira, 2008; Lewis, Pearce, & Bisson, 2012; D. Richards & Richardson, 2012; Riper et al., 2011; Spek et al., 2007). However, therapist support is requisite to improve effectiveness (Andersson & Cuijpers, 2009; Johansson & Andersson, 2012; Spek et al., 2007). Across studies, the type and frequency of therapist support may vary and range from minimal support, where a patient initiates contact, to telephone/e-mail or even face-to-face support (Barak, Klein, & Proudfoot, 2009). There are indications that a higher frequency of support leads to better effects (Johansson & Andersson, 2012). The first study on relapse prevention in partially remitted patients using an Internet-based Cognitive Behavior Therapy (CBT) was recently performed by Hollandäre and colleagues (2011; 2013). Over two years, lower relapse rates were found in the Internet-based CBT group compared with a control condition.

Chapters in part II

Chapter 6: meta-analysis preventive treatments

Well-known meta-analyses on prevention of relapse treatments mainly examined studies on C(B)T (Guidi et al., 2011; Piet & Hougaard, 2011; Vittengl et al., 2007). Only few studies examine other psychological treatments strategies, such as Interpersonal Therapy (IPT) (Vittengl et al., 2007). Further, evaluations on preventive Internet-based therapies and studies with booster sessions were not previously performed. Therefore, a meta-analysis including all randomized controlled trials on psychological treatments during (partial) remission was performed in chapter six. In addition to examining the effectiveness of psychological treatments, the influence of the number of previous episodes was taken into account. Information on which treatment strategies are the most effective and whether this is dependent on the number of previous episodes will help evidence based treatment guidelines for patients with recurrent depression.

Chapter 7, 8 and 9: Internet based psychotherapy

To examine whether Internet-based CT with minimal therapist support and monitoring by text messages and e-mail (Mobile CT) is effective in reducing relapse during remission (assessed with the Structured Clinical Interview of Axis I Disorders, DSM-IV criteria) (First, Spitzer, & Gibbon, 2001), a randomized controlled trial was performed. Mobile CT is based on the previously evaluated face-to-face Preventive CT (Bockting et al., 2005; Bockting et al., 2009). Mobile CT consists of eight sessions with a fixed structure and is a form of cognitive therapy adapted to prevent relapse in remitted but recurrently depressed patients. The details on the randomized controlled trial design and Mobile CT are described in chapter seven and nine. The short-term effects of Mobile CT on the secondary outcome, residual depressive symptoms, are described in chapter eight. Follow-up will be continued over two years to assess the primary outcome depressive relapse. In addition, in chapter nine a description of the usage of Mobile CT is provided.

Overview of the next chapters

The first part of this thesis focuses on the influence of childhood adversity and minor stress, chronic somatic illnesses and personality disorder on the longitudinal course of depression. Chapter two presents the results of our study on the premorbid vulnerability childhood adversity and its association with minor life stress sensitivity and the return of depressive symptoms in recurrently depressed patients. In this chapter we try to adress unanswered questions on whether premorbid vulnerability is related to depression after multiple episodes and whether this is mediated through heightened stress sensitivity. Chapter three and four consist of one systematic review and a systematic review including a meta-analysis on the influence of chronic somatic illnesses on depressive relapse and remission. We conclude the first part of the thesis with chapter five, which describes a potential way that personality disorder heightens the risk of returning of depressive episodes.

The second part of this thesis focuses on preventive treatment. In chapter six, a meta-analysis concerning the effectiveness of preventive treatments strategies in reducing the risk of relapse is presented. In chapter seven, the design of our

randomized controlled trial on Mobile CT is presented and in chapter eight and nine the short-term effects and usage of mobile CT are described.

Finally, in chapter ten, we discuss our research findings and the clinical implications.

Chapter 2

The scars of childhood adversity

Abstract

Background: Childhood adversity may lead to depressive relapse through its long-lasting influence on stress sensitivity. In line with the stress sensitization hypothesis, minor (daily) stress is associated with depressive relapse. Therefore, we examine the impact of childhood adversity on minor stress and its predictive value on prospectively assessed depressive symptoms in recurrently depressed patients. Method: Stress sensitivity was assessed in 309 recurrently depressed adult patients, enrolled into two randomized trials while remitted. Stress sensitivity was assessed at baseline as the reported intensity and frequency of dependent and independent daily stress. Independent stress is externally generated, by for example an accident happening to a friend, while dependent stress is internally generated, for example getting into a fight with a neighbor. Hierarchical regression analyses were performed with childhood adversity, independent and dependent daily stress as predictor variables of prospectively measured depressive symptoms after three months of follow-up. Results: We found that childhood adversity was not significantly associated with higher stress sensitivity. The intensity of both independent and dependent daily stress was predictive of depressive symptom levels at follow-up (unadjusted models respectively: B=0.47, t=2.05, p=0.041, 95% CI=0.02-0.92; B=0.29, t=2.20, p=0.028, 95% CI=0.03-0.55). No associations were found between childhood adversity and depressive symptoms at follow-up. Conclusion: No evidence was found supporting stress sensitization in this recurrently depressed but remitted patient group. Nevertheless, our research indicates that daily stress might be a target for preventive treatment.

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Introduction

Major Depressive Disorder (MDD) is a highly recurrent disease with reported relapse and recurrence rates that range from 50-90% (American Psychiatric Association, 2000; Burcusa & Iacono, 2007). Each depressive episode heightens the risk of additional relapses and recurrences (American Psychiatric Association, 2000; Consensus Development Panel NIMH/NIH, 1985; Kessing, Hansen, Andersen, & Angst, 2004; Solomon et al., 2000). For readability we refer to the more conservative term relapse in case of relapse and recurrence (Hollon et al., 2006). There is ample evidence that the experience of childhood adversity is related to the persistence of depression and depressive relapse, even after successful treatment (Hardeveld et al., 2013; Harkness, Bagby, & Kennedy, 2012; Nanni et al., 2012). More specifically, sexual abuse and emotional neglect seem to be associated with a poor prognosis of depression, and appear as independent determinants of chronicity of the disorder (G. W. Brown & Moran, 1994; Hovens et al., 2010; D. N. Klein et al., 2009; Wiersma et al., 2009). Knowledge on how childhood adversity leads to a poor prognosis of depression would provide insight into the causal processes and might help tailor treatment.

Vulnerability-stress

An explanation of childhood adversity, influencing the prognosis of depression, might be found in vulnerability-stress models (Abramson et al., 1989; Bleuler, 1963; Rosenthal, 1963; Zubin & Spring, 1977). Vulnerabilities, such as exposure to childhood adversity, are suggested to predispose someone to develop psychopathology after stress. Possibly, vulnerabilities cause heightened stress sensitivity on the long-term. Indeed associations are found between childhood adversities and an increased sensitivity to daily stressors in adult life (Comijs et al., 2007; Glaser et al., 2006; Wichers et al., 2009). This is supported by neurobiological studies as well, where a link between childhood adversities and epigenetic modifications to stress sensitivity has been demonstrated (Tyrka et al., 2012).

Stress sensitivity: stress, such as life events or daily stressors, is known as one of the most consistent predictors of respectively onset and relapse in MDD (Bockting et al., 2006; Kendler, Thornton, & Gardner, 2001; ten Doesschate et al., 2010).

According to the stress sensitivity or kindling hypothesis (Post, 1992), with increasing numbers of previous depressive episodes, the role of major life stress diminishes and minor daily life stress is considered as a more important predictor of depressive relapse (Bockting et al., 2006; Mazure, 1998; Monroe & Harkness, 2005). There is indeed evidence that minor life stress, such as the loss of personal belongings, plays a role in initiating the return of depressive symptoms and depressive episodes (Bockting et al., 2006; Monroe et al., 1996; Monroe et al., 2006; Ormel et al., 2001; ten Doesschate et al., 2010). So far, of the three studies that examined the impact of childhood adversities on stress sensitivity and subsequent depression, two demonstrated that the experience of childhood adversity was associated with higher stress sensitivity which successively heightened the risk of depression onset in adulthood (LaNoue et al., 2012; McLaughlin et al., 2010). Conversely, the third study found that childhood adversity did not lead to sensitivity to adult stress and therefore depression in an elderly cohort (55+ n=1887) (Comijs et al., 2007). Apart from the mere exposure to stress, McLaughlin and colleagues (2010) demonstrated that exposure to childhood adversity was related to a higher perceived intensity of adult daily stress. They suggest that a higher perceived intensity of stress could lead to negative mental health consequences after stress exposure.

Stress generation: according to the stress generation hypothesis of Hammen (1991), in which stress is potentially modifiable, characteristics and behaviors of persons themselves may lead to higher generation of stress. In this hypothesis, stress influenced by a person, such as having a disagreement, is defined as dependent stress and is considered to be more related to depression than externally generated independent stress, such as loss of a friend (i.e. stress generation; Hammen, 1991). In a recent study by Liu and colleagues (2013), the experience of childhood emotional neglect came forward as a unique predictor of dependent stress generation in participants with a history of depression, while independent stress was not a predictor. Depression itself is related to a heightened stress generation, even during remission (Hammen, 1991; Hammen, 2006). The influence of childhood adversity on stress could therefore eventually be overtaken by the influence of depression itself. Whether childhood adversity is associated to stress sensitivity, irrespective of previous episodes, is unknown.

Current study

In the current study we examine if an association between childhood adversity and the return of depressive symptoms exists in a currently remitted but recurrently depressed patient sample and if this is mediated by daily stress. We first studied if childhood adversity was related to 1) the return of depressive symptoms assessed at three month follow-up, 2) higher sensitivity to daily stress in general, and, depending on the actual presence of these associations, we examined 3) to what extent this was mediated by daily stress. Finally, additionally and aside from the mediation analysis, we examined 4) whether the reported frequency and intensity of daily stress was predictive of depressive symptoms at follow-up in recurrently depressed remitted patients. In line with Monroe et al. (2006), dependent and independent daily stress were examined separately to test for the stress generation hypothesis. We expected only dependent stress to be predictive of depressive symptoms after remission.

Method

Participants

The study sample consisted of 309 recurrently depressed patients that entered the study while remitted. They were recruited as part of two Randomized Controlled Trials (RCT) evaluating the effectiveness of Preventive Cognitive Therapy (PCT) to prevent relapse in depression. Trial A included remitted recurrently depressed patients (n=112) that used antidepressants and examines the effectiveness of face to face PCT in addition to or as alternative for antidepressant medication (ADM) versus ADM alone (for details see, Bockting et al., 2011). Trial B included remitted recurrently depressed patients (n=197) to examine the effectiveness of an online version of PCT in addition to Treatment as Usual (TAU) versus TAU alone (for details see, Bockting, Kok et al., 2011). There were no restrictions regarding the type or frequency of current TAU and TAU could consist of ADM treatment, primary care, secondary care or no treatment at all.

All participants were currently in remission at study start, for minimally two months but no longer than two years and experienced at least two depressive episodes in the past, assessed by the Structured Clinical Interview based on the Diagnostic and Statistical Manual of Mental Disorders (SCID-I; DSM-IV) (First et al.,

2001) and a score of 10 or below on the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$) (Hamilton, 1960). The SCID-I, administered by trained researchers over the telephone, was used to assess the number of previous Major Depressive Episodes (MDE), their timing and duration. The two most recent episodes of depression were assessed at symptom level in the SCID-I interview, in which the severity of an episode was established by assigning severity scores based on the number of symptoms (5 symptoms corresponds to mild, 6-7 symptoms corresponds to moderate, whereas 8-9 symptoms corresponds to severe depression). All other episodes were assessed by the core DSM-IV-TR criteria depressed mood (A1) or loss of interest (A2). The SCID-I was also used to exclude participants with: a) current or past mania or hypomania, b) current or past psychosis, c) current alcohol- or drug abuse, d) predominant anxiety disorder. Further exclusion criteria were recent electroconvulsive therapy and organic brain damage. All baseline data were acquired using online questionnaires before PCT took place. Both studies were approved by the Medical Ethical Committee and the participants provided informed consent.

Measures

Childhood adversities

Adversities before the age of 16 were assessed retrospectively by the Dutch version of the Life Events Questionnaire (LEQ) (Kraaij & de Wilde, 2001). Previous research rated the predictive validity of the LEQ as good (Kraaij & de Wilde, 2001). Emotional neglect and emotional abuse were not assessed by the LEQ. We assessed information with questions 5a, 12 and 13, respectively concerning the occurrence of a) death of a parent, b) being the victim of sexual abuse or, c) being the victim of physical abuse. Questions could be answered with yes (score=1) or no (score= 0). Although there is a variety of adverse events, many studies in this field focus on these specific events, which is why these were selected (Bockting et al., 2012; Hovens et al., 2010; Nemeroff et al., 2003; Spinhoven et al., 2010; Wiersma et al., 2009). A dichotomous variable was made, in which the presence of one or more of the adversities assessed with questions 5a, 12, and 13 were coded as 1, and the absence of all three was coded as 0.

Daily stress

The Dutch version of the Everyday Problem Checklist was used to assess the occurrence of 114 daily stressors in the three months preceding the baseline measurement (EPCL) (Vingerhoets & van Tilburg, 1994). The items were assigned to the subscales dependent stress (28 items) or independent stress (21 items) based on the manual of the EPCL (Vingerhoets & van Tilburg, 1994). A subdivision into these subscales is useful because dependent stress is said to be more related to recurrent depression (Harkness, Bruce, & Lumley, 2006). An example of a dependent event is you got into a conflict with a colleague, and an independent event is you had to wait long at an appointment. Additionally, the subscales total frequency and total intensity of dependent and independent stress were calculated in accordance to the manual of the EPCL. The intensity of daily stress describes how the impact of stressors is experienced and the score could range from 0 (no impact) to 3 (very much impact). The reliability of all the 114 EPCL items was α = .97, this was α = .79 for the dependent subscale (28 items) and α = .71 for the independent subscale (21 items).

Depressive symptoms

The Dutch translation of the Inventory of Depressive Symptomatology was used to measure depressive symptoms at baseline and three month follow-up ($IDS\text{-}SR_{30}$) (Rush et al., 1996). The inventory contains 30 items which can be answered on a 4-point scale, ranging from 0 (no symptom) to 3 (almost always troubled by symptom). The reliability of this measure according to Rush et al. (1986) was good (α. = .79 - .85). In this study the reliability was good as well (α = .77).

Statistical analyses

All analyses were performed using SPSS version 20.0 and we considered two-sided *p*-values <.05 to be statistically significant. The characteristics of the study populations of the two trials were compared[2].

[2] Chi square tests were used to test differences in dichotomous variables and independent sample T-Tests were applied to normally-distributed continuous variables, for non-normally distributed variables the non-parametric Mann-Whitney U statistic was used.

In order to account for missing data on depressive symptoms prospectively measured at three month follow-up, we used multiple imputation by chained equations, which is a state-of-the art technique because it reduces the chance of systematic bias due to non-random missing data (Schafer & Graham, 2002). Forty imputations were performed and were combined according to Rubin's rules (Rubin, 1987). We restricted the analyses to the group that was randomized to the control conditions of both trials (continuation of ADM and TAU) because the experimental treatment (PCT) could have interacted with the effect of childhood adversity or daily stress on depressive symptoms. Separate regression analyses were performed with either childhood adversity or daily stress included as the only independent variable in the first step of the model. In step two we adjusted for gender, treatment group (TAU or continuation of ADM) and in step three for the number of previous depressive episodes.

Female gender was adjusted for because it is positively associated with both stress and depression and is no intermediary variable (Liu & Alloy, 2010). The number of previous episodes of depression is one of the most important predictors of future depression (American Psychiatric Association, 2000) and could be considered a confounder. However, previous episodes may be part of the causal chain between childhood adversity and present depression and including previous episodes could imply overcorrection. Therefore, this variable was only included in the final supplementary step to investigate whether adversity was related to current depression independent of previous episodes. We did not control for baseline depressive symptoms as they were measured at the same time as daily stress and because of our interest in the associations with depressive symptom level rather than three months change.

If an overall association was found between childhood adversity and depression (Baron & Kenny, 1986), we performed another regression analysis with presence of childhood adversity entered in the first step and daily stress in the second step to examine if daily stress was a mediator of the possible relation between childhood adversity and depressive symptoms. The relative change in the regression coefficient for childhood adversity when daily stress was added as an independent variable was assumed to be a measure of mediation and was expressed as a percentage. The regression analyses were performed separately for dependent and independent daily stress and also for the daily stress intensity and frequency.

Results

Table 1 shows that most participants were female (68.6%) and had a mean age of 46.6 years (SD=10.6). Participants experienced a median of four previous depressive episodes (IQR =3.0) and were remitted for seven months on average (SD=6.2),. The baseline level of depressive symptoms was low, with a mean score of 3.6 (SD=2.8) on the HDRS17 (Hamilton, 1960) and a mean of 17.5 (SD=10.7) on the IDS-SR_{30}.

Table 1. Baseline demographic and clinical characteristics (n = 309)

	Total (N=309)	Trial A (N=112)	Trial B (N=197)	p^a
Age, mean (SD)	46.6 (10.6)	47.4 (9.8)	46.1 (11.0)	.281
Female gender, no. (%)	212/309 (68.6)	70/112 (62.5)	142/197 (72.1)	.097
ADM at recruitment, no. (%)				.000
No ADM	95/307 (30.9)	0/112 (0.0)	95/195 (48.7)	
Yes ADM	212/307 (69.1)	112/112 (100.0)	100/195 (51.3)	
Current psychotherapy	62/256 (24.2)	28/111 (25.2)	34/145 (23.5)	.304
Age of first MDD episode, mean (SD)	29.10 (12.7)	28.63 (12.7)	29.30 (12.6)	.657
Previous episodes MDD, median (IQR)	4.0 (3.0)	4.0 (3.0)	4.0 (2.0)	.087
Depressive symptomatology HDRS17	3.60 (2.8)	3.39 (2.7)	3.79 (2.9)	.242
Depressive symptomatology (IDS-SR_{30})	17.47 (10.7) (n=294)	18.85 (11.2) (n=107)	16.67 (10.3) (n=187)	.092
Severity last episode				
Minor (%)	64/308 (20.8)	13/111 (11.7)	51/197 (25.9)	.003
Moderate (%)	160/308 (51.9)	58/111 (52.3)	102/197 (51.8)	
Severe (%)	84/308 (27.3)	40/111 (36.0)	44/197 (22.3)	
Daily stress, mean (SD)				
Dependent frequency	13.41 (9.86)	9.75 (5.0)	9.94 (4.9)	.757
Dependent intensity	13.26 (9.8)	12.60 (10.1)	13.65 (9.7)	.135
Independent frequency	6.08 (3.4)	6.05 (3.6)	6.09 (3.3)	.500
Independent intensity	7.85 (6.3) (n=269)	7.83 (7.4) (n=99)	7.87 (5.6) (n=170)	.603
Childhood adversity no. (%)				
Loss of a parent	16/274 (5.8)	6/103 (5.8)	10/171 (5.9)	1.000
Physical abuse	35/274 (12.8)	13/103 (12.6)	20/171 (11.7)	.849
Sexual abuse	33/274 (12.0)	10/103 (9.7)	25/171 (14.6)	.267

Note, [a]*p*-value based on chi-square statistic for categorical variables and analyses of variance for continuous variables and the Mann-Whitney U for previous episodes of MDD ADM=Antidepressant medication; MDD=Major Depressive Disorder; HDRS17=17-item Hamilton Rating Scale for Depression; IDS-SR_{30}=Inventory of Depressive Symptomatology.

Almost one fourth of the participants reported having experienced childhood adversities (22.6%, n=274). The trials did not differ on any of the demographic and clinical characteristics, except for ADM use. Because participants in trial A had to use antidepressants continuously in the last six months to be included in the study this led to significant differences with regard to ADM use and the rate of visiting a general

practitioner between trial A and B. Furthermore, there was a statistically significant difference between severity of the last depressive episode in both groups, with a higher number of participants having a severe previous episode in trial A (36% versus 22.3%).

The TAU and continuation of ADM group

Of the total group, n=138 participants were assigned to the TAU group (n=82, Trial B) and continuation of ADM group (n=56, Trial A) of which n=40 (29%) participants suffered at least one childhood adversity. At baseline there were no significant differences between mean depressive symptoms scores (IDS-SR_{30}) for the combined TAU and continuation of ADM group and the PCT group (respectively: M=17.72 SD=11.1; M=17.49, SD=10.2 *p*=0.855). However the mean depressive symptom scores at three months follow-up were significantly higher in the combined TAU and continuation of ADM group than in the PCT group (respectively: M=20.70, SD=11.3; M=16.95, SD=12.7, *p*=0.016). There were no significant differences with regard to depressive symptom measured three months after remission between the TAU and continuation of ADM groups (trial A: M=20.11, SD=12.4; trial B: M=21.10, SD=13.3; *p* =0.678) and these data were merged.

In the combined TAU and continuation of ADM group we estimated the pooled standard deviation (SD) of the IDS-SR_{30} to be 13. Given this SD it was possible to detect moderate or larger effects (d = 0.53 or over) given 40 subjects with and 100 subjects without a history of childhood adversities, a two-sided alpha of 0.05 and a beta of 0.8.

Regression analyses

Childhood adversity did not significantly predict depressive symptoms at three months follow-up (B=4.073, t=1.522, *p*=0.128, 95% CI=-1.18-9.33). Addition of any of the other variables in the next steps did not lead to any significant changes in this model. The R^2 and adjusted R^2 are small (respectively 0.048 and 0.019) indicating that only a small part in the variance of depressive symptoms is explained by the included variables.

The presence of childhood adversity was not related to any of the daily stress subscales(*r*=-.007-.087). Therefore, we did not proceed to the analysis of a mediating role of daily stress.

Table 2. Hierarchical regression model of the TAU and continuation of ADM group for the prediction of depressive symptoms at 3-month follow-up from childhood adversity (n=138)

Variable		B	t	95% CI	R^2 Change
Step 1					0.023
	(Constant)	19.535	14.044**	[16.81, 22.26]	
	CA presence	4.073	1.522	[-1.18, 9.33]	
Step 2					0.007
	(Constant)	19.727	4.967**	[11.94, 27.51]	
	CA presence	4.035	1.504	[-1.23, 9.30]	
	Female gender	1.553	0.629	[-3.29, 6.40]	
	Treatment group	-0.874	-0.371	[-5.50, 3.75]	
Step 3					0.002
	(Constant)	15.540	3.154**	[5.88, 25.20]	
	CA presence	4.046	1.515	[-1.20, 9.29]	
	Female gender	1.029	0.417	[-3.81, 5.87]	
	Treatment group	-0.827	-0.353	[-5.42, 3.77]	
	Number of previous episodes	3.176	1.430	[-1.18, 7.53]	

Note, CA= Childhood adversity; R^2 final model = 0.048, Adjusted R^2 = 0.012;* p < 0.05,** p < 0.01.

Daily stress as a predictor of depressive symptoms at follow-up

All baseline daily stress subscales showed moderate to high correlations among themselves (r=.414-.819, *p*<0.01) and with baseline depressive symptoms (*r*=.308-.399, *p*<0.01). To prevent the loss of explained variance in depressive symptoms, four separate regression analyses were performed for each daily stress subscale (table 3a-3d). Both the reported intensity of independent- and dependent daily stress significantly predicted depressive symptoms at three months follow-up (respectively: B=0.470, t=2.046, *p*=0.041, 95% CI=0.02-0.92; B=0.291, t=2.202, *p*=0.028, 95% CI=0.03-0.55). After adjustments in the next steps, these results did not change significantly. Frequency of independent and dependent daily stress did not significantly predict depressive symptoms and again these results did not significantly change after adjustments. The R^2 of all the total models was small (0.044-0.073) as were the adjusted R^2 of the total models (0.015-0.045), meaning only a small part of the variation in prospectively depressive symptoms in remitted recurrently depressed patients was explained by the variables in the model.

Table 3a. Hierarchical regression model of the TAU and continuation of ADM group for the prediction of depressive symptoms at 3-month follow-up from independent stress intensity (n=138)

Variable		B	t	95% CI	R^2 Change
Step 1					0.039**
	(Constant)	17.244	8.423**	[13.23, 21.26]	
	Independent stress, intensity	0.470	2.046*	[0.02, 0.92]	
Step 2					0.009
	(Constant)	16.185	3.609**	[7.39, 24.98]	
	Independent stress, intensity	0.488	2.086*	[0.03, 0.95]	
	Female gender	2.244	0.910	[-2.59, 7.08]	
	Treatment group	-0.415	-0.177	[-5.01, 4.18]	
Step 3					0.025
	(Constant)	10.768	1.967*	[0.33, 24.50]	
	Independent stress, intensity	0.533	2.279*	[0.07, 0.99]	
	Female gender	1.676	0.684	[-3.13, 6.48]	
	Treatment group	-0.315	-0.136	[-4.87, 4.24]	
	Number of previous episodes	3.785	1.711	[-0.55, 8.12]	

Note, R^2 final model = 0.073, Adjusted R^2 = 0.045; * $p < 0.05$, ** $p < 0.01$.

Table 3b. Hierarchical regression model of the TAU and continuation of ADM group for the prediction of depressive symptoms at 3-month follow-up from dependent stress intensity (n=138)

Variable		B	t	95% CI	R^2 Change
Step 1					0.044
	(Constant)	17.024	8.261**	[12.98, 21.07]	
	Dependent stress, intensity	0.291	2.202*	[0.03, 0.55]	
Step 2					0.005
	(Constant)	17.001	3.936**	[8.53, 25.47]	
	Dependent stress, intensity	0.284	2.138*	[0.02, 0.54]	
	Female gender	1.257	0.514	[-3.54, 6.05]	
	Treatment group	-0.525	-0.223	[-5.13, 4.08]	
Step 3					0.016
	(Constant)	13.218	2.542*	[3.02, 23.42]	
	Dependent stress, intensity	0.276	2.086*	[0.02, 0.54]	
	Female gender	0.781	0.319	[-4.02, 5.58]	
	Treatment group	-0.492	-0.210	[-5.08, 4.09]	
	Number of previous episodes	2.954	1.343	[-1.36, 7.27]	

Note, R^2 final model = 0.064, Adjusted R^2 = 0.036; * $p < 0.05$, ** $p < 0.01$.

Table 3c. Hierarchical regression model of the TAU and continuation of ADM group for the prediction of depressive symptoms at 3-month follow-up from independent stress frequency (n=138)

Variable		B	t	95% CI	R^2 Change
Step 1					0.022
	(Constant)	17.321	6.907**	[12.40, 22.24]	
	Independent stress, frequency	0.561	1.554	[-0.15, 1.27]	
Step 2					0.009
	(Constant)	16.569	3.459**	[7.17, 25.96]	
	Independent stress, frequency	0.591	1.609	[-0.13, 1.31]	
	Female gender	2.138	0.860	[-2.74, 7.01]	
	Treatment group	-0.617	-0.261	[-5.25, 4.01]	
Step 3					0.023
	(Constant)	11.292	1.960	[-0.01, 22.59]	
	Independent stress, frequency	0.659	1.800	[-0.06, 1.38]	
	Female gender	1.598	0.646	[-3.25, 6.45]	
	Treatment group	-0.531	-0.227	[-5.13, 4.06]	
	Number of previous episodes	3.631	1.631	[-0.74, 8.00]	

Note, R^2 final model = 0.054, Adjusted R^2 = 0.026; * $p < 0.05$, ** $p < 0.01$.

Table 3d. Hierarchical regression model of the TAU and continuation of ADM group for the prediction of depressive symptoms at 3-month follow-up from dependent stress frequency (n=138)

Variable		B	t	95% CI	R^2 Change
Step 1					0.018
	(Constant)	17.440	6.703**	[12.34, 22.54]	
	Dependent stress, frequency	0.337	1.427	[-0.13, 0.80]	
Step 2					0.007
	(Constant)	17.543	3.800**	[8.49, 26.60]	
	Dependent stress, frequency	0.339	1.428	[-0.13, 0.80]	
	Female gender	1.673	0.675	[-3.19, 6.53]	
	Treatment group	-0.888	-0.376	[-5.52, 3.74]	
Step 3					0.018
	(Constant)	13.361	2.430*	[2.58, 24.15]	
	Dependent stress, frequency	0.339	1.435	[-0.12, 0.80]	
	Female gender	1.150	0.465	[-3.70, 6.00]	
	Treatment group	-0.841	-0.358	[-5.45, 3.76]	
	Number of previous episodes	3.171	1.428	[-1.18, 7.53]	

Note, R^2 final model = 0.044, Adjusted R^2 = 0.015; * $p < 0.05$; ** $p < 0.01$.

Discussion

Our first research aim was to investigate the influence of childhood adversity on the depressive symptoms three months after remission and whether adult daily stress was a mediator of this potential influence. We found no support for our hypothesis that childhood adversity predicts depressive symptoms. Additionally, in contrast to our hypothesis, childhood adversity was not related to daily stress in later life either. This is at odds with previous research where childhood adversity led to higher later life stress sensitivity which in turn predicted the onset of depression (LaNoue et al., 2012; McLaughlin et al., 2010). However, this is the first investigation of the effect of childhood adversity on daily stress and prospectively measured depressive symptoms in recurrently depressed patients while remitted. Importantly, these findings have to be interpreted in the context of our highly recurrent study sample. With a median of four previous depressive episodes (IQR=3.0), a potential effect of childhood adversity on risk of relapse might have been overshadowed. Unfortunately, we cannot compare this to other related studies, because in comparable studies overall the information on the mean or median number of previous depressive episodes was not mentioned (Collishaw et al., 2007; Ritchie et al., 2009; Suija, Aluoja, Kalda, & Maaroos, 2011; Wainwright & Surtees, 2002).

Alternatively, different pathways could lead from childhood adversity to depressive relapse. Cognitive variables such as dysfunctional attitudes may play a role, given that they develop early in life and the occurrence of childhood adversities is presumed to negatively influence their development (Beck, 1967). Evidence for this pathway was found in previous research in patients with a history of depression, where a negative cognitive style was a mediator in the relation between childhood adversity and stress generation (Liu et al., 2013). More research is needed to specify this potential pathway in recurrent depression.

A final research aim was to examine if daily stress was predictive of depressive symptoms measured three months after baseline remission. In line with previous research, (McLaughlin et al., 2010), we found intensity of dependent and independent daily stress to be predictive of subsequent depressive symptoms after remission. Although we expected only dependent stress to be predictive, our finding is consistent with the study of Monroe et al. (2006). In their study, 126 recurrently depressed patients were followed over three years of maintenance treatment, where

'subject focused independent daily stress' (an event that happens to a person self instead of an acquaintance or relative) was predictive of depressive relapse. Abramson, Seligman & Teasdale (1978) suggested that independent stress poses a risk for depressive relapse because of the lack of control on individual experiences when independent events occur which heightens the stress response.

Strengths and Limitations

While it is an advantage to study this high risk of relapse patient group to determine whether childhood adversity and daily stress influence the return of depression, the downside is that the experience of previous episodes could make the detection of pathways from childhood adversity to depressive relapse difficult. The following limitations have to be taken into account.

First, the level of depressive symptoms at three-month follow-up is relatively low since patients were remitted at study start which could make finding an effect difficult. Second, the limited follow-up time of three months and relatively small sample size may lower the chance of detecting an effect. However, based on the number of patients with-, versus without exposure to childhood adversity, detection of a moderate to large effect seemed possible. Although this standard deviation was derived out of our own study, it was comparable to other MDD populations (Schulte-van Maaren et al., 2013). Third, while retrospective assessment of childhood adversity is representative, irrespective of presence of mental illness even up to 20 years (Lizardi & Klein, 2005), self-report is said to lead to less strong associations than contextual measures (R. C. Kessler, Davis, & Kendler, 1997). Alloy, Liu and Bender (2010) state that using a self-report checklist as assessment tool of stressful life events could lead to more interpretative biases by patients and the lack of contextual information makes it hard to differentiate between dependent and independent events. Furthermore, information about the intensity and frequency of childhood adversity is missing, but could be decisive with regard to long-lasting influences on stress and depression. Fourth, there is a wide variety of other types of childhood adversity that were not assessed but could be of importance. For example emotional neglect and emotional abuse were not assessed in our study, although they are potentially important to the prognosis of depression (G. W. Brown & Moran, 1994; Hovens et al., 2010; Wiersma et al., 2009). Additionally, previous research in patients with a history of depression showed that specifically emotional neglect was

the significant predictor of prospective negative dependent events (Liu et al., 2013). Fifth, the participants in this study were recruited for two studies that differed with respect to ADM use and the mean severity of the previous depressive episode. Although we controlled for treatment group, these differences still may have influenced the results. Sixth, the low level of variance in depressive symptoms explained by intensity of daily stress suggests the existence of other predictors of depressive symptoms.

Conclusion and future directions

Our study suggest that the perceived intensity of daily stress is a predictor of depressive symptoms three months after remission, which heightens the risk of relapse in recurrently depressed patients. The intensity of daily stress is potentially modifiable and could therefore be a treatment aim in the prevention of depressive relapse, irrespective of experienced childhood adversity.

There is an indication that PCT reduces the negative influence of daily stress on depressive relapse (Bockting et al., 2006; ten Doesschate et al., 2010), but more information on the course of daily stress is required to examine long-term treatment effects on daily stress and relapse. Other studies with a larger sample size and a longer follow-up time are needed to replicate these findings and to examine other potential pathways of childhood adversity to depressive relapse, including cognitive variables.

Chapter 3

Comorbid chronic somatic illness and depressive relapse

Abstract

Objective: To perform a systematic review, and if possible a meta-analysis, to establish whether depressed patients with comorbid chronic somatic illnesses are a high risk "double trouble" group for depressive recurrence. Method: The databases PubMed, EMbase and PsycINFO were systematically searched until the 4th of December 2012 by using MeSH and free text terms. Additionally, reference lists of retrieved publications and treatment guidelines were reviewed, and experts were consulted. Inclusion criteria were: depression had to be measured at least twice during the study with qualified instruments and the chronic somatic illness had to be assessed by self-report or by a medical professional. Information on depressive recurrence was extracted and additionally risk ratios of recurrence were calculated. Results: The search generated four articles that fulfilled our inclusion criteria. These studies showed no differences in recurrence over one- two- three- and 6.5 years of follow-up for a total of 2010 depressed patients of which 694 patients with a comorbid chronic somatic illness versus 1316 patients without (Study 1: RR= 0.49, 95% CI, 0.17-1.41 at one year follow-up and RR=1.37, 95% CI, 0.78-2.41 at two year follow-up; Study 2: RR=0.94, 95% CI, 0.65-1.36 at two year follow-up; Study 3: RR=1.15, 95% CI, 0.40-3.27 at one year follow-up; RR=1.07, 95% CI, 0.48-2.42 at two year follow-up and RR=0.99, 95% CI,0.55-1.77 at 6.5 years follow-up; Study 4: RR=1.16, 95% CI, 0.86-1.57 at three year follow-up). Conclusion: We found no association between a heightened risk for depressive recurrence and comorbid chronic somatic illnesses. There is a need for more longitudinal studies to justify the current specific treatment advice such as long-term pharmacological maintenance treatment for this presumed "double trouble" group.

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Introduction

Major Depressive Disorder (MDD) has a highly recurrent nature (Judd, 1997) with relapse and recurrence rates rising up to 85% (Mueller et al., 1999). Recurrence is defined as a new Major Depressive Episode (MDE) after recovery, that is at least six months without meeting full MDE criteria, whereas relapse is the return of a MDE during remission but before recovery (1988, MacArthur Foundation Research Network on the Psychobiology of Depression) (Frank et al., 1991).

Most frequently used international evidence based clinical practice guidelines i.e. National Institute for Health & Care Excellence (NICE) (2009), American Psychiatric Association (APA) (2010), presume that comorbid chronic general somatic disorders are associated with poorer outcomes of depression including an increased risk of recurrence (for readability we always refer to recurrence in case of relapse or recurrence).

Depression is more prevalent in people suffering somatic illness, with prevalence rates being two (Moussavi et al., 2007) to even three times as high as for people without somatic illness (American Psychiatric Association, 2010; Egede, 2007). Depression has been associated with poorer outcomes of somatic illness (Egede, 2007; Evans & Charney, 2003; National Institute for Health & Care Excellence, 2010; Tossani, Cassano, & Fava, 2005), in terms of more functional disability, higher care consumption and a lower quality of life (Noël et al., 2004). Conversely, the presence of a comorbid chronic somatic condition is perceived as an ongoing stressor that predisposes patients to depressive episodes (American Psychiatric Association, 2010). The APA (2010) describes “the presence of a chronic general medical disorder” (pp 58) as a risk factor for recurrence of MDD and therefore recommends that “some form of maintenance treatment will be required indefinitely” (pp 19).

Objectives

Remarkably, there are no reviews or meta-analyses that examined the effect of comorbid chronic somatic illness on depressive recurrence. Given the impact of current international clinical guidelines, we aim to systematically review the evidence as to whether somatic illness is a risk factor for recurrences of MDD over a period of

at least six months. If possible a meta-analysis will be performed as well (depending on the number of studies and their methodological characteristics).

Method

Inclusion criteria

Inclusion criteria for our review were: (1) longitudinal measurement of the course of depression (2) providing absolute numbers or percentages of recurrence a) diagnosis established with an interview based on state- of the- art depression criteria (e.g. Diagnostic and Statistical Manual of Mental Disorders, DSM-III/III-R/DSM-IV) (American Psychiatric Association, 1994; American Psychiatric Association, 1980; American Psychiatric Association, 1987), or b) with standardized questionnaires that assess depressive symptoms (e.g., Inventory of Depressive Symptomatology, IDS) (Rush, Gullion, Basco, & Jarrett, 1996) or -, Hamilton Rating Scale for Depression, (HRSD) (Hamilton, 1960) (3) with a follow-up of at least six months (4) in which data were collected for patients with and without a certain comorbid chronic somatic illness at the same measurement intervals a) where comorbid chronic somatic illnesses were assessed either via self-report or b) medical records or c) by a diagnosis of a medical professional. There is great overlap between self-report of somatic illnesses and diagnoses of these illnesses (Wallace & Herzog, 1995), therefore studies that used self-report as a measurement tool were included as well. If treatment effects were studied within a randomized controlled trial without a treatment-as-usual group, these were excluded. We also excluded studies on bipolar disorders. All relevant publications in English, Dutch, Spanish, Polish or German were taken into account. To assess eligibility of articles, one reviewer (GK) made the first selection based on titles. In case of doubt, abstracts or full text articles were retrieved for closer reading. Thereafter, two independent reviewers made a selection based on abstracts (GK and WH); further winnowing was performed by two reviewers (GK and CB) based on full text articles. In case of inconsistencies, articles were evaluated again until consensus was reached. The kappa statistic for inter-observer variability was reported for the abstract and full-text selection.

Literature search

In line with the APA (2010) and NICE (2009), treatment guidelines we limited the search to chronic somatic illnesses. The chronic somatic illnesses chosen for this systematic review were: heart diseases, gastrointestinal diseases, diabetes mellitus, rheumatoid arthritis, asthma, Human Immunodeficiency Virus (HIV) and neoplasms. The choice of these chronic somatic illnesses was based on them being mentioned in the clinical practice guidelines of the APA (2010) and NICE (2009), and their high prevalence rates brought up in additional literature (Koike et al., 2002; Simon, Von Korff, & Lin, 2005). A combination of MeSH-terms and free text words was entered into the search engines PubMed, EMbase and PsycINFO. These were all screened for relevant articles through 4 December 2012. The terms ‘depression or depressive disorder or major depression were combined with heart diseases or gastrointestinal diseases or diabetes mellitus or arthritis, rheumatoid or asthma or HIV or neoplasms and incidence or follow-up studies or prognos* or predict* or course or outcome or relaps* or recur* or remis* or epidemiology. The key words regarding depression outcomes were based on Altman (2001) (box 2) and modified by adding relaps*, recur* and remis* to fit our research purpose. Since not all studies might explicitly mention recurrence, even though they studied the impact on for example chronicity, including recurrence, we decided on the above mentioned broad search terms. Additionally, reference lists from included articles, earlier reviews and NICE and APA clinical treatment guidelines (2010; 2010; 2009), were screened for other potentially eligible papers and experts were consulted to identify additional important papers.

Data extraction and outcomes

The following data were extracted from the included articles: study site, number of participants, their age and gender distribution, information about depression assessment (method and measurement intervals), characteristics of the chronic somatic illnesses (type and assessment method) and the outcome measure (recurrence). Outcomes consisted of the differences in percentages or mean numbers of recurrence during follow-up, if applicable for multiple time intervals, between patients with and without comorbid chronic somatic illness. Risk ratios (RR) and 95% Confidence Intervals (CI) were calculated by using Review Manager 5.1.

Quality assessment

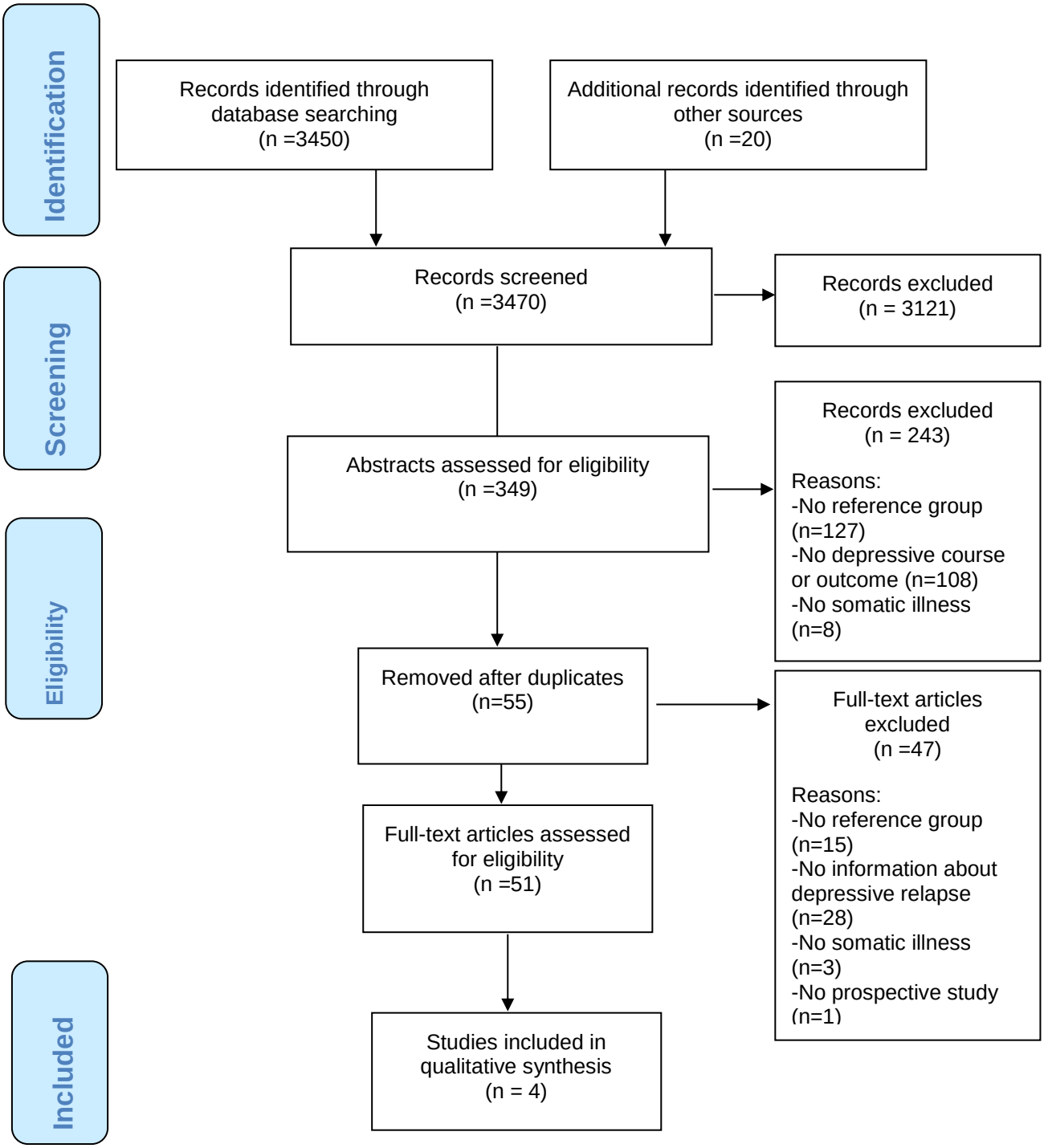
To allow for judgments on the quality of the included articles regarding their selection process, design, analyses and outcome measures, a modified version of the Newcastle-Ottowa Quality Assessment Scale for cohort studies was used (Deeks et al., 2003; G. Wells, Shea, O'Connell, Peterson, & Welch). This instrument was reviewed by Deeks et al. (2003) and described as one of the most usable methods for this type of study (Deeks et al., 2003; Reeves, Deeks, Higgins, & G. Wells, 2008; 2008). All articles were judged by two reviewers (GK and WH). If information on a quality criterion was not mentioned explicitly in the article, we assigned a question mark (see table 2).

Results

Study selection

As shown in Figure 1, the search engines yielded 3450 articles in total. Twenty records were identified via additional sources including APA guidelines (n=6), experts (n=2), reference lists from subsequently included articles (n=10), and important reviews (n=2). After screening based on title done by one reviewer (GK), 3121 articles were excluded. Main reasons for exclusion based on title were: studies reported about the influence of depression in a somatic illness population only or about the prevalence of depression only. A total of 349 abstracts subsequently were screened by two independent reviewers (GK and WH). After removal of 55 duplicate titles, eventually 51 full text articles were retrieved for close reading. Detailed information on reasons for exclusion is shown in the flow diagram (Figure 1). Finally, four articles about recurrence of depression in patients with and without comorbid chronic somatic illness were included. The Kappa statistic for the inter-observer variability was 0.91.

Figure 1. PRISMA flow chart of the study selection



Data extraction from included studies

Data were extracted for the four articles with a total number of 2010 patients (n=554 in study 1, n=715 in study 2, n=54 in study 3, and n=687 in study 4), yielding information on 694 patients (34.5%) who suffered one or more chronic somatic illness. Table 1 gives an overview of the data extracted from the four studies.

Study characteristics

Study 1: A non-experimental longitudinal follow-up study by Wells, Rogers, Burnam, and Camp (1993) with adults who received care in one of the following settings: “large group-practice-style health maintenance organizations (HMOs), large multispecialty mixed prepaid and fee-for-service group practices, and small single-specialty group and solo practices”. Patients with either a current depressive disorder or depressive symptoms where included (n=554 patients). A depressive disorder was defined as meeting DSM-III criteria (American Psychiatric Association, 1980) for a lifetime diagnosis of MDD or dysthymia, an episode of MDD or dysthymia during the past 12 months, with no remission since the onset of the recent episode. Depressive symptoms were present when the cut-off score on a brief depression screener was exceeded (Burnam, Wells, Leake, & Landsverk, 1988). According to the authors (personal communication), patients were asked how many episodes they experienced over follow-up with at least a two month break of depressive symptoms between episodes. The group consisted of 21 (3.8%) patients who suffered current Insulin-Dependent Diabetes Mellitus (IDDM) and 533 (96.2%) without IDDM. Two other somatic illnesses and their relation with depressive recurrence were studied by Wells et al. (1993) however we only used the information on the IDDM group while this was the only current chronic somatic illness mentioned.

Table 1. Data extraction and outcomes of the four included studies

Authors (publication year)	Number of patients	Age	Gender, female (%)	Depression assessment 1) Baseline 2) Follow-up	Illness assessment	Outcome measures	Results
Wells, Rogers, Burnam & Camp (1993)	554 total (3.8% SI, 96.2% NSI)	-	73.8% (IDDM) 72.8% (non-IDDM)	1) Eight- item depression symptom scale, DSM III criteria 2) Course of depression interview over the telephone, based on DIS	Screening and structured somatic history interview	Percentage of patients with more than two depressive spells during 9.9 years of follow-up	1 year: SI: 14.9% NSI: 29.3% 2 year: SI: 36.0% NSI: 27.8%
Gerrits, van Oppen, van Marwijk, van der Horst & Penninx (2012)	715 total (44.5% SI 55.5% NSI)	42.1[a]	66.0%	1) CIDI, DSM IV 2) CIDI, DSM IV and Life Chart Inventory	Self-report	Percentage of patients with remission with recurrence of symptoms (at least three months symptom-free interval)	2 year: SI: 6.0% NSI: 8.0%
Kovacs, Goldston, Obrosky & Drash (1997)	54 total (44.4% SI, 55.6% NSI)	11.2[a]	61.9%	1) ISCA, DSM-III 2) ISCA, DSM-III	Diagnoses at hospital	Recurrence rates: cumulative proportion of developing a new episode of depression after recovery	1 year: SI: 26.0% NSI: 22.0% 2 year: SI:30.0% NSI: 32.0% 6.5 year: SI: 47.0% NSI: 47.0%
Hardeveld, Spijker, De Graaf Nolen & Beekman, 2012	687 total (48.2%SI, 51.8% NSI)	40.7[b]	68.0%	1) CIDI, DSM-III-R 2) CIDI, DSM-III-R retrospectively and prospectively at T1 or T2	Self-report, list of 31 mostly chronic somatic conditions	MDE recurrence between baseline and follow-up (one-or three years) for patients in partial or complete remission for at least six months	SI: 21.1% NSI: 18.3%

Note, SI=Somatically Ill; NSI=Non-Somatically Ill; [a] = mean age; [b]= median age; IDDM= Insulin-Dependent Diabetes Mellitus; DSM III/III-R/IV criteria= Diagnostic and Statistical Manual of Mental Disorders, third edition, third edition revised; fourth edition; DIS=Diagnostic Interview Schedule; CIDI= Composite International Diagnostic Interview; ISCA= Interview schedule for children and adolescents; MDE=Major Depressive Episode.

Study 2: The study of Gerrits, van Oppen, van Marwijk, van der Horst and Penninx (2012) is a cohort study (ages 18-65 years) that consisted of 1209 adult participants with a current depression or anxiety diagnosis as assessed by using the Composite International Diagnostic Interview (CIDI) (Wittchen et al., 1991), based on DSM-IV criteria (American Psyciatric Association, 1994), followed across two years. Only the information on depression recurrence was used (received through personal communication with the authors), which resulted in data on 715 patients with depression. A total of 318 patients (44.5%) had one or more of the following chronic somatic diseases: cardio-metabolic, respiratory, musculoskeletal, digestive, neurological, endocrine and cancer.

Study 3: Kovacs, Obrosky, Goldston, and Bonar (1997) included 54 children (ages 8-13 years) in their longitudinal follow-up study. There were 24 children (44.4%) with current IDDM and 30 children (55.6%) with no other somatic disorders from the same children's hospital. MDD was assessed with the semi structured Interview Schedule for Children and Adolescents (ISCA) (Kovacs, 1985). The control subjects without somatic comorbidity and a first MDE were balanced for age of onset of first MDD, other comorbidities and basic characteristics. Of the 24 participants with comorbid IDDM, six (25%) already suffered from a major psychiatric disorder (i.e. n=4 with anxiety disorder, n=1 conduct disorder and n=1 with functional enuresis). The follow-up period was almost ten years (mean of 9.9 years). Recovery was defined as not fulfilling criteria for MDE, i.e. the absence of symptoms or the presence of few subclinical symptoms, and persistence of this state for at least two months. Of the participants with IDDM, 21 (87.5%) recovered from a first episode as for 29 (96.7%) of the control group.

Study 4: Hardeveld, Spijker, De Graaf, Nolen and Beekman (2013) included 687 patients from the general population (ages between 18-64 years). Of the total group, 331 patients (48.2%) had a somatic disease, which was assessed by a questionnaire including 31, mostly, chronic somatic illnesses during the past 12 months. To be included in the study, patients had to be in partial or complete remission of MDD and/or dysthymia for at least six months and the amount of months of being in remission could differ between patients. Remission was defined as: not meeting the full MDE criteria and was assessed at baseline by the computerized version of the CIDI (Wittchen et al., 1991). MDE recurrence was assessed between baseline and three year follow-up. Recurrence was defined as the return of a MDE after partial or

complete remission of at least six months. The authors provided us with the absolute numbers of MDE recurrence for patients with and without a somatic illness. Information on the quality criteria for all four included studies is presented in Table 2.

Table 2. Quality assessment of the included studies according to a modified version of the Newcastle-Ottowa Quality Assessment Scale for cohort studies

Domain	Wells, Rogers, Burnam & Camp (1993)	Gerrits, van Oppen, van Marwijk, van der Horst & Penninx (2012)	Kovacs, Goldston, Obrosky & Drash (1997)	Hardeveld, Spijker, De Graaf, Nolen & Beekman (2012)
Representativeness of cohort	*	*	-	*
Selection of the non-exposed cohort	*	*	?	*
Ascertainment of exposure	-	*	*	-
Comparability of groups with and without somatic illness on basis of design or analysis	*	*	*	*
Assessment of depression at baseline (blinding demanded)	-	?	-	-
Assessment of depression at follow-up (blinding demanded)	-	-	-	-
Follow-up at least 6 months?	*	*	*	*
Adequacy of follow-up of cohorts	?	?	?	-

Note, *=rated as meeting the quality criterion, -=rated as not meeting the quality criterion; ?=no information about quality criterion.

Risk Ratios

In Table 3 and Figure 2, an overview of the number of recurrences in both the patients with and without somatic illness are presented and the RRs of the four studies at all the follow-up intervals are shown in a forest plot.

As shown in Table 1 the reported recurrence rates in Wells et al. (1993) are lower at the one year follow-up but higher at the two year follow-up in the current IDDM group compared to the group without IDDM (14.9% vs. 29.3 % at one year follow-up; 36.0% vs. 27.8 % at two year follow-up). The calculated RR at one year follow-up is far below one, which might indicate less risk for recurrence of depression in the IDDM patients (n=21) in comparison to the non-IDDM patients (n=533). However, at two year follow-up there is a shift to a somewhat higher than one RR, indicating more risk for depressive recurrence in the IDDM patients compared to the non-IDDM patients. In the IDDM group, the calculated RRs at one-

and two year follow-up are based on recurrences of three and eight patients respectively. Also, the fact that the 95% CI contains the score of one in both cases leads us to conclude that there is no higher risk for two or more depressive episodes for patients with comorbid IDDM compared to patients without comorbid IDDM (RR=0.49, 95% CI, 0.17-1.40; RR=1.37, 95% CI, 0.78-2.41).

Among the 715 participants in the study by Gerrits et al. (2012), 57 (8.0%) of the participants who did not have a comorbid chronic somatic illness experienced a recurrence after remission versus 43 participants (6.0%) who did have one or more comorbid chronic somatic illnesses. The RR of having one or more chronic somatic illnesses was around one (RR= 0.94, 95% CI, 0.65-1.36) meaning that in this sample there was no higher risk of recurrence after remission for patients with comorbid chronic somatic illnesses.

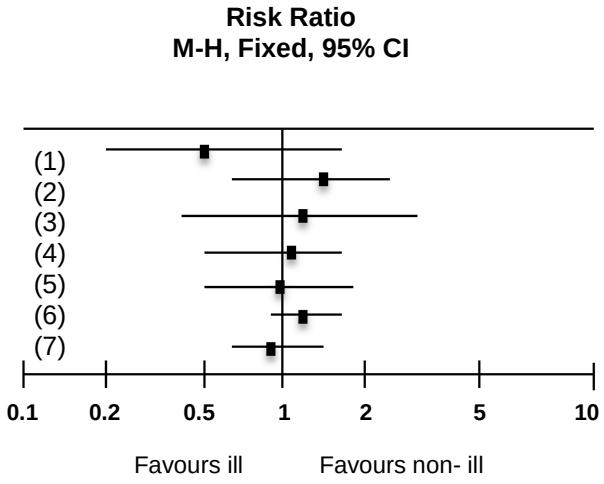
Kovacs et al. (1997) found similar recurrence rates in the illness group at one, -two -and 6.5 years of follow-up (respectively: 26% in the somatic illness group versus 22% in the control group; 30% in the somatic ill versus 32% in the control condition; 47% in both the somatically ill and the control condition). RRs range from 0.99-1.15, which again is around one and indicates that the presence of comorbid IDDM therefore did not seem to heighten the risk of recurrence in this group at one-, two-, and 6.5 year follow-up respectively (RR=1.15, 95% CI, 0.40-3.27; RR=1.07, 95% CI, 0.48-2.42; RR= 0.99, 95% CI, 0.55-1.77).

In the study of Hardeveld et al. (2013), 135 patients (19.7%) experienced a recurrence. The median time to recurrence was six years (SD=5.5). MDE recurrence rate was 21.1% for patients with a somatic illness compared to 18.3% for patients without a somatic illness. The RR of MDE recurrence was close to one (RR=1.16, 95% CI, 0.86-1.57). This indicates that there is no significant heightened risk for a depressive recurrence, between baseline and three years of follow-up, for patients with a comorbid somatic illness in comparison to patients without a comorbid somatic illness.

Table 3. Number of recurrences and risk ratios in somatic ill and non-somatic ill for all four included studies

		Somatic ill		Non-somatic ill				
Study name	Follow-up (years)	Recurrence	Total	Recurrence	Total	Risk ratio	Lower limit	Upper limit
Wells, 1993 (1)	1	3	21	156	533	0.49	0.17	1.40
Wells, 1993 (2)	2	8	21	148	533	1.37	0.78	2.41
Kovacs, 1997 (3)	1	5	21	6	29	1.15	0.40	3.27
Kovacs, 1997 (4)	2	7	21	9	29	1.07	0.48	2.42
Kovacs, 1997 (5)	6.5	10	21	14	29	0.99	0.55	1.77
Hardeveld, 2012 (6)	3	70	331	65	356	1.16	0.86	1.57
Gerrits, 2012 (7)	2	43	318	57	397	0.91	0.65	1.36

Figure 2. Forest plot of the risk ratios of depressive recurrences with comorbid chronic somatic illness for all four included studies



Discussion

The aim of this systematic review was to determine whether having a comorbid chronic somatic illness in MDD predicts a greater risk of depressive recurrence. Only four studies examined recurrence in patients with- and without comorbid chronic somatic illnesses. Surprisingly, there was no indication that comorbid somatic illness was associated with a greater risk for recurrence.

Strengths and limitations

We applied broad search terms and inclusion criteria, and acquired studies through three important databases, reference lists, guidelines and experts in the field. This led to the identification of a large number of articles that were reviewed in a systematic fashion by multiple reviewers. Most studies failed to meet the inclusion criteria, mainly because they did not include a reference group without a somatic illness. Rather, these studies presented results of depression and its course within a specific disease group only. Presence of a reference group is crucial in order to draw conclusions on the risk ratio for recurrence that is associated with comorbid somatic illness.

The included studies differed to a large extent in their methodological characteristics. Therefore it was not appropriate to do a meta-analysis and calculate a pooled risk ratio. The included studies had methodological problems; the quality assessment shows some of these limitations. Whereas baseline depression was defined by DSM criteria in all four studies, that was not the case with respect to depressive recurrence at follow-up in the study by Wells et al. (1993). Wells et al. (1993) assessed the number of patients with more than two depressive episodes during follow-up. Episodes were defined as periods of depression separated by at least two months of intervening remission as reported by the patient; no DSM criteria were applied to each separate episode. This is not in accordance with the other three studies that did identify each separate episode of depression by applying DSM criteria. Additionally, these episodes cannot be directly compared to MDE recurrences as reported in Gerrits et al. (2012), Kovacs et al. (1997) and Hardeveld et al. (2013). On the other hand, since Wells et al. (1993) reported exclusively more than two episodes during follow-up, the actual rate of recurrences could have been underestimated. Gerrits et al. (2012) used a life chart assessment to minimize the risk of missing possible recurrences (Lyketsos, Nestadt, Cwi, & Heithoff, 1994). Depressive symptomatology fluctuates over time (Judd, 1997) and can be easily overlooked if assessed only at fixed time points, like they did in three out of the four studies (Hardeveld et al., 2013; Kovacs et al., 1997; K. B. Wells et al., 1993). In addition, there are several differences between the studies that further complicated drawing firm conclusions on the overall effect of somatic illness on recurrence rates, such as, different follow-up times, received treatment, type and assessment method

of somatic illnesses, depressive symptomatology at baseline, unequal sizes of somatic illness and reference groups (the most unequal sample had 21 somatic ill patients versus 533 patients without somatic illness in the study of Wells et al, 1993). Also there were differences in the choice and sizes of the reference groups (533, 397, 30 and 356 patients).

Implications

Current clinical guidelines, such as the APA and the NICE, identified the group of MDD patients with comorbid chronic somatic illness as a “double trouble” group with poor prognosis (American Psychiatric Association, 2010; National Institute for Health & Care Excellence, 2010; National Institute for Health and Care Excellence, 2009). Prolonged pharmacological maintenance treatment has been recommended for these patients if they were treated with antidepressants during the acute phase of their depressive episode. Additional preventive psychological treatment was recommended for those who received psychotherapy during acute treatment. However, our review suggests that the number of studies that could provide such evidence is very small and that those few studies that are available provide no indication of any elevated risk of recurrence among depressed patients with comorbid somatic illness. We therefore call for additional longitudinal studies about the impact of comorbid chronic somatic illness on the course of depression. Apart from recurrence, other outcomes also are potentially relevant, such as the quality of life, severity and duration of episodes, hospitalization, sick leave from work and persistence of depression. An interesting question might be whether the prognosis of depression could deteriorate when somatic illness progresses and if so, whether treatment of the somatic illness can counter this process. Additionally, we need to study whether maintenance pharmacotherapy’s, as well as psychological interventions, are (equally) effective for this presumed high risk group regarding recurrence.

Chapter 4

Comorbid chronic somatic illnesses and depressive remission

Abstract

Objective: This study aimed to systematically review and meta-analytically evaluate studies on prospectively assessed remission of a depressive episode, in individuals with versus without chronic somatic illnesses. Data sources: A literature search using the following search terms was performed using PubMed, EMbase and PsycINFO: 'depression or depressive disorder or major depression' and 'heart diseases or gastrointestinal diseases or diabetes mellitus or arthritis, rheumatoid or asthma or HIV or neoplasms' and 'incidence or follow-up studies or prognos or predict* or course or outcome or epidemiology relaps* or recur* or remis*'. Additionally, experts in the field, treatment guidelines and systematic reviews were consulted. Study selection: Data were obtained on cohort studies reporting on (non-)remission of a depressive episode, i.e. rates, time to, or duration of (non-)remission for both individuals with and without a chronic somatic illness. Five studies on 1431 individuals were included in the meta-analysis. Data extraction: For each available remission outcome, Risk Ratios (RR) were calculated. The pooled risk of non-remission in somatically ill individuals was calculated using a random-effects model. Results: One out of the five included studies found evidence for a higher risk of non-remission in depressed individuals with comorbid somatic illness (RR=2.08, 95 % CI: 1.30-3.34; p=0.002). The pooled RR showed no significant differences in non-remission between individuals with and without comorbid somatic illness (RR=1.13; 95% CI: 0.79-1.60; p=0.51). However, substantial heterogeneity between studies was found (I^2= 69%). Conclusion: After an extensive search, these findings imply that there is no decisive evidence that chronic somatic illness is associated with an elevated risk of non-remission in depression. There is a serious lack of information on the prognosis of depression in individuals with comorbid chronic somatic illness.*

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Introduction

Chronic somatic illnesses are often comorbid with depression (9-23%) (Moussavi et al., 2007). There is ample evidence of depression having an adverse impact on the prognosis of chronic somatic illnesses (Anderson, Freedland, Clouse, & Lustman, 2001; Crum, Cooper-Patrick, & Ford, 1994; Moussavi et al., 2007; Patten, 1999; K. B. Wells, Golding, & Burnam, 1988). The reverse relationship is also presumed, with chronic somatic illnesses increasing the likelihood of poorer outcomes in depression (American Psychiatric Association, 2010; National Institute for Health & Care Excellence, 2010). Remission and recovery[3] of Major Depressive Disorder (MDD) are mentioned as the most important aim in known clinical practice guidelines for the treatment of MDD (for an overview: American Psychiatric Association, 2010; Rush, 1995). It is of note that (partial) persistence of depression (non-remission) is not only very disabling for a patient, but is also a risk factor of depressive relapse and recurrence (Rush, 1995). Two reviews have been conducted on studying the association between somatic illness and persistence of depression. In the majority of included studies in both reviews, a significant association between somatic illnesses and depressive non-remission was found. However, the first one was a non-systematic and narrative review (Cole, Bellavance, & Mansour, 1999) while the other (Licht-Strunk, van der Windt, van Marwijk, de Haan, & Beekman, 2007), included studies that did not include a reference group (Denihan et al., 2000) and did not assess the presence of a somatic illness at (Kennedy, Kelman, & Thomas, 1991). Therefore, the conclusions of these reviews have to be treated with caution. To the best of our knowledge, there are no other systematic reviews or meta-analyses in this field. Therefore, we performed a systematic review and meta-analytically evaluated (non-)remission in studies reporting on MDD individuals with and without a chronic somatic illness. Compared to non-somatically ill individuals we expected lower remission rates, a longer time to remission, briefer depression-free spells, and a longer duration of depressive episodes in chronic somatically ill individuals.

[3] Remission is defined as less than 6 months free of depression and recovery as more than six months free of depression (Frank, Prien, Jarrett, & Keller, 1991).

Method

Selection criteria

We systematically searched for articles reporting on (non-)remission of a depressive episode, i.e. rates, time to, or duration of (non-)remission for both individuals with and without a chronic somatic illness. Remission or recovery was defined as not meeting all depression diagnostic criteria or not exceeding the cut-off score of an established self-report questionnaire. We searched for cohort studies with a minimal follow-up time of six months in adult individuals aged 18 or older and without restrictions to study setting. To be included in the review, presence or absence of depression or depressive symptoms had to be assessed at baseline and follow-up in the same study with a) an interview based on state-of-the-art depression criteria (e.g. Diagnostic and Statistical Manual of Mental Disorders, DSM-III/III-R/DSM-IV) or b) with standardized questionnaires that assess depressive symptoms using specific cut-off scores (e.g., Inventory of Depressive Symptomatology, IDS) (Rush et al., 1986, 1996). Somatic illnesses had to be assessed at baseline and had to be chronic, such as heart diseases, gastrointestinal diseases, diabetes mellitus, rheumatoid arthritis, asthma, Human Immunodeficiency Virus (HIV) and neoplasms (Koike et al., 2002; Simon et al., 2005). Chronic somatic illnesses were assessed by a) patient self-report or b) medical records or c) a diagnosis by a medical professional. All publications in English, Dutch, Spanish or German were included. Effect sizes had to be expressed as risk ratios or allowed for conversion into risk ratios. If this was not the case, the corresponding authors were asked by e-mail or telephone to provide us with effect sizes, or the number of cases of (non-)remission. In case of absence of authors' response after at least four attempts, the article was excluded from further analysis.

Literature search

Search terms regarding the depression outcomes were based on Altman (2001) (box 2). The following MeSH-terms and free text words were entered in the search engines of PubMed, EMbase and PsycINFO: 'depression or depressive disorder or major depression' and 'heart diseases or gastrointestinal diseases or diabetes mellitus or arthritis, rheumatoid or asthma or HIV or neoplasms' and 'incidence or

follow-up studies or prognos* or predict* or course or outcome or epidemiology relaps* or recur* or remis*'. In addition to using the search engines, we reviewed reference lists from the included articles, earlier systematic reviews and meta-analyses (Cole et al., 1999; Evans et al., 2005; Licht-Strunk et al., 2007) as well as the American Psychiatric Association (APA) and National Institute for Health & Clinical Excellence (NICE), clinical practice guidelines of treatment of MDD (2010, 2009). Finally, experts in the field were consulted to identify relevant articles. The selection of articles was based on meeting the inclusion and exclusion criteria. Articles were reviewed for eligibility until 29 April 2013 in three steps: 1) based on their titles by one reviewer (GK), where in case of doubt abstracts or full text articles were retrieved for further reading, 2) based on their abstract by two independent reviewers (GK and WH), and 3) based on the full text articles by two independent reviewers (GK and WH), where in case of doubt a third reviewer (PC or CB) was consulted for advice. The inclusion of articles took place until consensus was reached.

Quality assessment

We used the Newcastle-Ottowa Quality Assessment Scale for cohort studies (G. Wells et al., cited 15 November 2012) to assess the quality of included studies. This instrument came forward as one of the best applicable instruments in prospective cohort studies in a review by Deeks et al. (2003). Small scale modifications were made by the reviewers in order to allow for judgments on the selection and comparability of the participants with and without a somatic illness as well as on the quality of outcome measures. Study quality of all articles was independently judged by two reviewers (GK and WH). In case of doubt a third reviewer was consulted (CB). When information on a quality criterion was missing or not explicitly mentioned a question mark was assigned. A star was assigned when a quality criterion was met, and a minus was assigned when a study did not meet a quality criterion. For the criterion 'assessment of depression' at baseline and follow-up we assigned a star if an interview was used that based on state of the art questionnaires or diagnostic criteria.

Statistical Analysis

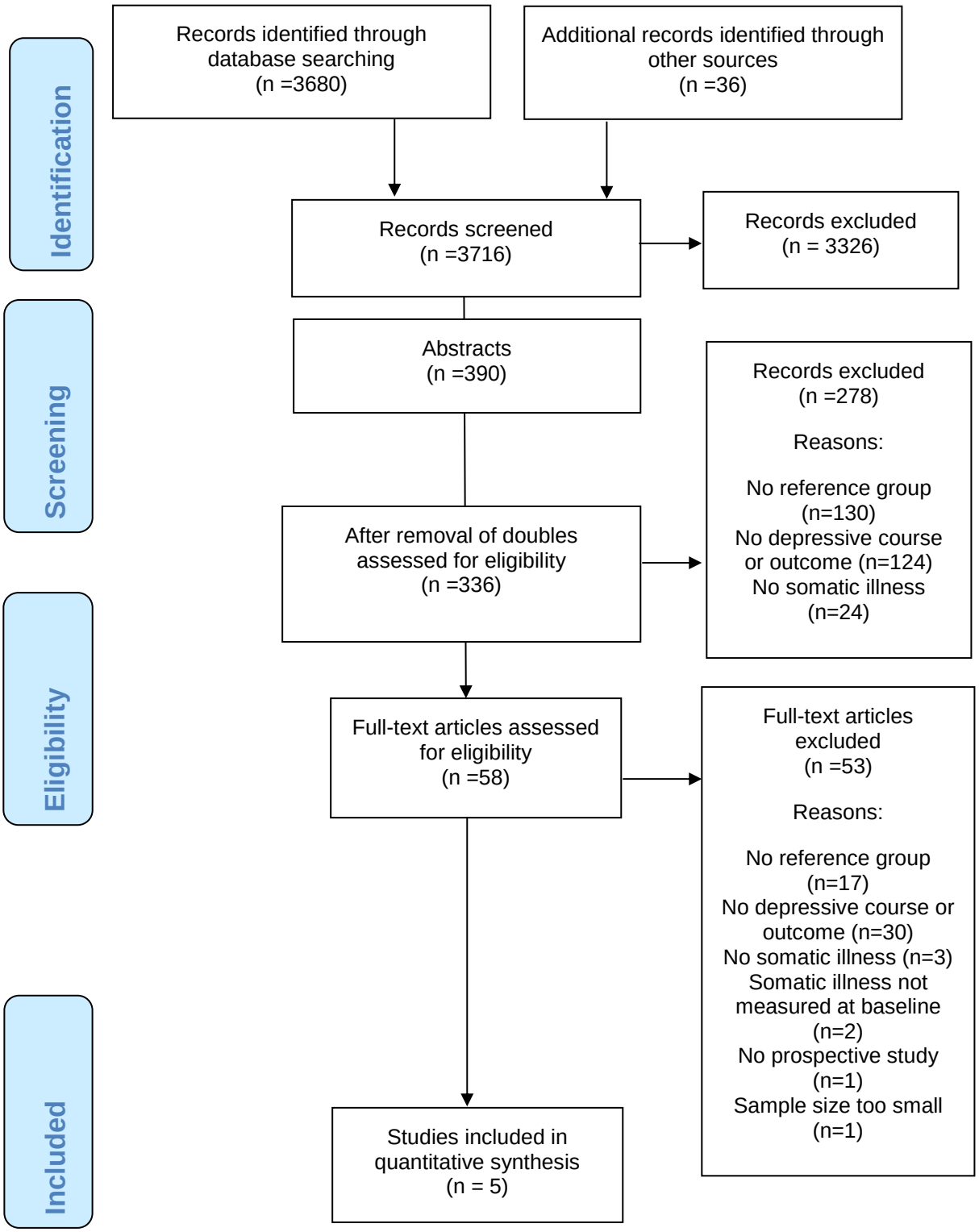
Risk ratios (RR) and 95% Confidence Intervals (CI) were calculated by Review Manager 5.1. for each separate depression outcome per study. If Hazard Ratios (HR) were available these could be considered as a RR because it is possible to interpret these outcomes in the same way (Deeks, Higgins, & Altman, 2008). We made sure that all effect sizes were in the same direction by inversing them when needed, with a RR above one indicating an increased risk of non-remission when chronic somatic illness is present. The RRs, HRs and 95% CIs of each remission related outcome was entered in a spreadsheet of Comprehensive Meta-Analysis 2 software (CMA) (Borenstein, 2005). Calculation of the pooled mean effect size was performed using DerSimonian en Laird's random effects model, and a forest plot was produced additionally (Borenstein, Hedges, Higgins, & Rothstein, 2009). To assess heterogeneity of included studies we calculated the I-square statistic. This statistic can be interpreted as the proportion of total variation across studies due to heterogeneity rather than chance (Higgins, Thompson, Deeks, & Altman, 2003; Higgins & Thompson, 2004). When the I-square statistic was higher than 50% heterogeneity was considered to be significant (Higgins et al., 2003). Depending on the amount of included studies and available depression outcomes, when high heterogeneity was found sensitivity analyses were performed.

Results

A total of 3680 articles were found using the search engines. Thirty-six additional articles could be retrieved via reference lists of the APA (2010) and NICE treatment guidelines (2010; 2009) as well as from reviews and experts in the field, leading to a total amount of 3716 hits. Most articles could be excluded based on title alone (n=3326), because studies reported depression in a somatically ill population only, or they only reported prevalence of depression. In Figure 1 a flow chart of the identification of studies that could be included is depicted. Exclusion after reading abstracts (n=336) or full-text articles (n=58) mostly took place when studies did not report on any depression outcomes (n=154), or when a reference group without a chronic somatic illness was missing (n=147). Finally, five articles matched the

inclusion criteria and reported on remission and the time to remission in individuals with and without a chronic somatic illness.

Figure 1. Flow chart of study identification



Study characteristics

Data on a combined total of N=1431 adults was available of which n=640 (44.7%) had been diagnosed with a comorbid somatic illness. The chronic somatic illnesses assessed at baseline in all five studies were very diverse (e.g. cancer, diabetes mellitus, cerebrovascular diseases). The quality assessment for each study is presented in Table 1. The main characteristics of each study are described below.

Spijker, de Graaf, Bijl, Beekman, Ormel and Nolen (2004) described the results of the Netherlands Mental health Survey and Incidence Study (NEMESIS). The study sample consisted of 250 participants (18-64 years) from the general population diagnosed with a Major Depressive Episode (MDE). At baseline first incidence or recurrent episodes were assessed with the Composite International Diagnostic Interview (CIDI) (Robins et al., 1988). With three month intervals, the Life Chart Interview (LCI) (Lyketsos et al., 1994), was used to assess duration of MDE which was the outcome of interest. Chronic somatic illnesses during the past 12 months were assessed with a self-report questionnaire including 31 mostly chronic illnesses for which participants received treatment (Bijl, van Zessen, Ravelli, de Rijk, & Langendoen, 1997).

Gerrits, van Oppen, van Marwijk, van der Horst and Penninx (2012) reported data of the Netherlands Study of Depression and Anxiety (NESDA) which is a large cohort study (ages 18-65 years). The two-year follow-up data on 715 participants diagnosed with MDD at baseline, assessed with the CIDI, were used. Chronic somatic illnesses were assessed by self-report and were only taken into account if a patient received treatment for it. Outcome of interest was the time to recovery or remission.

Van den Brink, Ormel, Tiemens, Smit, Jenner, van der Meer and van Os (2002) reported the one-year follow-up data of 269 participants with baseline MDD assessed according to ICD-10 criteria (World Health Organization, 1993). The outcome of interest was non-recovery during one year follow-up as assessed with the CIDI Primary Health Care Version (CIDI-PHC) (Tiemens, VonKorff, & Lin, 1999). Chronic somatic illnesses were assessed by questions on absence or presence of multiple somatic illnesses that were added to the baseline CIDI-PHC interview (Von Korff, 1995).

Licht-Strunk, van Marwijk, Hoekstra, Twisk, de Haan and Beekman (2009) performed a longitudinal cohort study (The West Friesland Study) about depressive outcomes in participants aged 55 years and over with a MDD diagnosis at study start. The three year follow-up data on recovery in n=96 participants were used, with assessments every six months. We extracted information on recovery which was assessed with the Montgomery Asberg depression rating scale (range 0-60) (Montgomery & Asberg, 1979), and the primary care evaluation of mental disorders (range 0-9) (Spitzer, Williams, Kroenke, & Linzer, 1994). Chronic somatic illnesses were assessed with a self-report questionnaire consisting of a list of chronic somatic illnesses such as heart disease or respiratory disease. The self-report list originated from the study of Kriegsman and colleagues (1996).

Riihimäki, Vuorilehto, Melartin and Isometsä (2011) reported the five year follow-up data of the Vantaa Primary Care Depression Study of n=102 participants (20-69 years) with a MDD DSM-IV diagnose at baseline. Chronic medical illnesses were assessed with a self-report questionnaire, medical records and an interview. A somatic illness was only defined as present if the condition had been diagnosed by a doctor. The checklist was originally used by Finnish National Insurance Institutions. The outcome measure of interest was the duration of the index depressive episode and was assessed with the Structural Clinical Interview for DSM-IV TR Axis I Disorders (First et al., 2001) and a life-chart (Melartin et al., 2004; Vuorilehto, Melartin, & Isometsä, 2009).

Table 1. Quality assessment of the included studies according to a modified version of the Newcastle-Ottowa Quality Assessment Scale for cohort studies

Domain	Spijker, (2004)	Gerrits, (2012)	Van den Brink, (2002)	Licht-Strunk, (2009)	Riihimäki, (2011)
Representativeness of cohort	*	*	*	*	*
Selection of the non- exposed cohort	*	*	*	*	*
Ascertainment of exposure	-	*	*	-	*
Comparability of groups with and without somatic illness on basis of design or analysis	?	*	?	?	?
Assessment of depression at baseline	*	*	*	?	*
Assessment of depression at follow-up	*	-	*	?	*
Follow-up at least 6 months?	*	*	*	*	*
Adequacy of follow-up of cohorts	*	?	?	?	?

Note, *=fulfills the criterion; -=does not fulfill the criterion; ?=unsure if the criterion is fulfilled, not mentioned explicitly in the article.

Data extraction from the included studies

All five studies reported data on (non-)remission or (non-)recovery (in other words duration of a depressive episode) and therefore these outcomes could be compared and pooled. The definitions for recovery and remission in the included studies varied. Spijker et al. (2004) did not differentiate between remission and recovery but did require a minimum amount of three months without meeting criteria of MDD. In the studies of both Gerrits et al. (2012) and van den Brink et al. (2002) minimum duration of six month of not fulfilling diagnostic criteria of depression was required to establish remission or recovery. Riihimäki et al. (2011) defined remission as a period of at least two months of not meeting DSM-IV criteria. The article of Licht-Strunk et al. (2009) did not supply information about a minimum amount of time in which participants had to be depression-free. Because of these differences, a distinction between remission and recovery was not made. For readability, we will use the term remission to describe our results. HRs and their 95% CIs were available and extracted from the articles of Licht-Strunk et al. (2009) and Riihimaki et al. (2011)

They included somatic illness as a predictor of non-remission in their model and absence of somatic illness as the reference category. In order to calculate RRs for the remaining studies, absolute numbers regarding remission were received through personal communication with Spijker et al. (2004), Gerrits et al. (2012) and van den

Brink et al. (2002). We made sure that all HRs and RRs pointed in the same direction, in this case meaning that a HR or RR higher than one indicated a longer time to remission or a higher risk of non-remission in the chronic somatically ill group. Table 2 presents an overview of the study characteristics and outcomes for the chronic somatically and non-somatically ill. Overall, most RR or HR values were around one, indicating no difference between the patient groups with and without a chronic somatic illness. There was one study by van den Brink and colleagues (2002) that found an effect below one, indicating an association between the presence of comorbidity and a higher chance on remission (RR=0.68, 95% CI=0.41-1.11, *p*=0.129). However, this effect was not significant. Only Spijker and colleagues (2004) found a significant higher risk of non-remission to be associated to presence of a comorbid chronic somatic illness (RR=2.08, CI=1.30-3.35, *p*=0.002).

Table 2. Study characteristics and depression outcomes for individuals with versus without chronic somatic illnesses

Author	Somatic illness	Outcome	Non-somatic illness	Outcome	Definition and assessment of outcome	Follow-up (yrs)	Extra information
Spijker et al. 2004	n=133	Non recovery 45/133	n=117	Non recovery 19/117	Recovery: No or minimal depressive symptoms in 3-months LCI	2 years	RR=2.08 (1.30-3.35)
Gerrits et al.2012	n=317	Longer time to remission 65/317	n=397	Longer time to remission 73/397	Late sustained remission: Not fulfilling DSM-IV criteria of MDD>6 months CIDI and LCI	2 years	RR=1.12 (0.83-1.51)
Van den Brink et al. 2002	n=70	Non recovery 15/70	n=199	Non- recovery 63/199	Non-Recovery: Still depressed during 1 year follow-up -no 50% reduction in depressive symptoms (number of symptoms -duration of baseline episode > 6 months CIDI	1 year	RR=0.68 (0.41-1.11)
Licht-Strunk et al.2009	n=66	Prediction of non-recovery 1 illness vs. 0: HR=1.22 (0.72-2.04)	n=30	Prediction of non-recovery reference group survival analysis	Recovery: -Montgomery Asberg depression rating scale cut-off of <10 -not fulfilling DSM criteria of MDD	3 years	HR=1.22 (0.72-2.04)
Riihimaki et al.2011	n=54	Longer time to full remission Somatic illness as predictor: HR=0.81, CI=0.50-1.30)	n=48	Longer time to full remission reference group in analysis	Remission: Not meeting DSM-IV criteria for MDD for at least two months SCID-I, life chart	5 years	HR = 0.81 (0.50-1.30)

Note, LCI=Life Chart Interview; CIDI=Composite International Diagnostic Interview; MDD=Major Depressive Disorder; DSM/DSM-IV=Diagnostic and Statistical Manual of Mental Disorders; SCID-I= Structured Clinical Interview for DSM-IV Axis I Disorders.

Pooled outcome

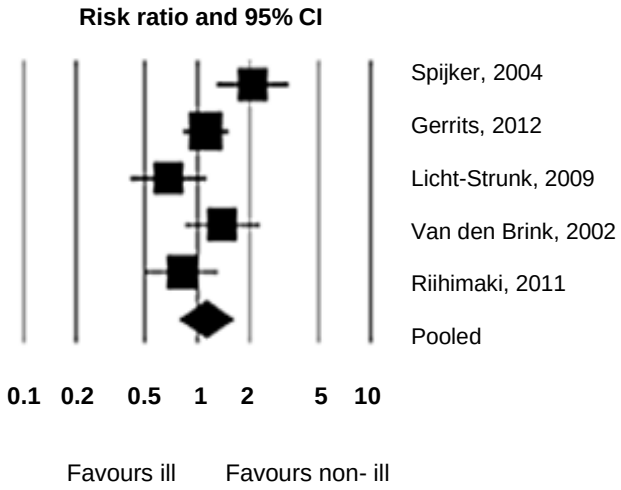
Because all study outcomes could be assigned to the category non-remission, a pooled RR was calculated by CMA. Table 3 and Figure 2 show the RRs and their 95% CI, Z-value and *p*-value for each separate study as well as for the pooled outcome. Based on the pooled data of all five studies there is no significantly higher risk of a longer time to remission or a higher risk of non-remission in chronic somatically ill individuals (RR=1.13; 95% CI: 0.79-1.60; *p*=0.51). However, the I-square was 69% suggesting a significant moderate to high heterogeneity (Higgins et al., 2003) between the five studies. Thus, it could be possible that the pooled outcome effect is attributable to difference between the studies instead of chance. In order to examine reasons for heterogeneity, the analysis was repeated without the study of Spijker et al. (2004). Since this study was an outliner with respect to significance of RR results which may have accounted for the high variability between studies. To explore this possibility, the study of Spijker et al. (2004) was excluded after which the I-square fell to 43.7%, which is still moderate to high but non-significant. The pooled effect of all studies without the study of Spijker et al. (2004) again was around one (RR=0.98, 95% CI: 0.74-1.31, *p*=0.91). Therefore, there is no evidence for an association between chronic somatic illness and a longer time to remission or a higher risk of non-remission. However, due to high variability between studies these results are uncertain. Given the low number of included studies we did not investigate these differences by other sensitivity analyses.

Table 3. Pooled effect of the five included studies

Study name	Statistics for each study				
	Risk ratio	Lower limit	Upper limit	Z	*p*
Spijker, 2004	2.080	1.296	3.339	3.033	0.002
Gerrits, 2012	1.120	0.830	1.511	07.42	0.458
Van den Brink, 2002	0.680	0.413	1.119	-1.518	0.129
Licht-Strunk, 2009	1.390	08.52	2.272	1.314	0.189
Riihimaki, 2011	0.810	0.502	1.306	-0.864	0.387
Pooled	1.126	0.791	1.601	0.658	0.510

Note, 1= higher risk of non-remission or longer time to remission in non- somatically ill
>1= higher risk of non-remission or longer time to remission in somatically ill.

Figure 2. Forest plot and pooled effect of the five included studies



Discussion

Main findings

Depression with a chronic somatic illness is presumed to increase the likelihood of poorer depression outcomes as stated in leading clinical guidelines (American Psychiatric Association, 2010) (pp 19, 21, 58). A systematic review including a meta-analysis was carried out to evaluate whether a comorbid chronic somatic illness in depression is indeed associated with a poor prognosis in terms of remission (i.e. time to remission, remission rates, duration of remission). Five studies did meet our inclusion criteria and examined (non-)remission or (non-)recovery in MDE individuals with versus without a chronic somatic illness. Overall there were no significant differences between depressed individuals with-, versus without a somatic illness in time to remission or risk of non-remission. As such, there is no convincing evidence that presence of chronic somatic illness is associated to worsened remission related outcomes. In addition, in a previous systematic review (Kok et al., 2013), we found no evidence for a heightened risk on depressive relapse and recurrence in the chronic somatically ill after remission. These findings are not in line with earlier reviews and the assumption of the clinical practice guidelines in which chronic somatic illness is said to be related to a poorer course of depression (e.g. American Psychiatric Association, 2010; Cole et al., 1999;

Evans et al., 2005; Licht-Strunk et al., 2007; National Institute for Health & Care Excellence, 2010). However, we performed an extensive systematic search in which we only included studies that contained both a reference group without a somatic illness as well as a baseline measurement of chronic somatic illness. Furthermore, only studies measuring depression at least twice within the same study were included to capture the fluctuating course of depression by prospective assessment (Beekman et al., 2002; Licht-Strunk et al., 2007).

Limitations

The results have to be considered in light of the limitations of this systematic review and its included studies. First, although all included studies had a minimal follow-up time of at least one year with a maximum of five years (Riihimäki et al., 2011), it is still possible that fluctuations of depression have not been captured fully due to its dependency on the moment of assessment and the applied timeframe. Second, there were differences between the required duration of depression-free time that the included studies used to define remission or recovery. In one study (Licht-Strunk et al., 2009), a minimum duration of time that was spent depression-free was not mentioned at all. Differentiating between remission and recovery was not possible given the different definitions. However, it could have been of importance, given that a longer period of being depression-free may protect against depressive relapse or recurrence (Dunlop, Holland, Bao, Ninan, & Keller, 2012). Third, we found substantial heterogeneity between the five studies which suggests that the pooled effect may have been affected by variability between studies, which may have biased our conclusions. The high heterogeneity could be caused by the study of Spijker et al (2004) which was an outlier. However, the heterogeneity remained substantial after removal of the study of Spijker et al (2004) and findings have to be considered with caution. As factors threatening study comparability we assume the following: differences between study setting (primary care and community), ages of participants (with one study conducted in a 55+ population, Licht-Strunk et al., 2009), follow-up times, treatment and types of somatic illnesses. In addition, it is questionable if all chronic somatic illnesses have the same impact on depression. Future large-scale studies are needed to examine this. Given the small

number of included studies, stratification of the analyses by these differences was not deemed meaningful. Further, bias was not formally examined due to the low number of included studies. Fourth, the quality assessment showed that information on the comparability and adequacy of follow-up measurement of somatically and non-somatically ill individuals was missing in all studies. This uncertainty should be taken into account when interpreting the results. Finally, four out of the five included studies were conducted in the Netherlands, although not based on the same cohort studies. Thus, future studies need to clarify to what extent our findings can be generalized across various national health care systems.

Implications

An extensive systematic search led to only five available studies that examined (non-)remission of depression in individuals with and without a chronic somatic illness. This demonstrates a serious lack of data regarding this topic and underscores the necessity to study the impact of comorbidity of a chronic somatic illness on the course of depression (Gerrits et al., 2012; Kok et al., 2013; Vuorilehto et al., 2009). The majority of the included studies did not find that the presence of a comorbid somatic illness was associated with a higher risk of non-remission.

These findings indicate that currently there is no compelling evidence that the presence of chronic somatic illness is associated with a poorer prognosis of depression.

Chapter 5

Personality and Cognitive Vulnerability

Abstract

Background: Personality Disorders (PDs) have been associated with a poor prognosis of Major Depressive Disorder (MDD). The aim of the current study was to examine cognitive vulnerability (i.e., dysfunctional beliefs, extremity of beliefs, cognitive reactivity, and rumination) that might explain poor prognosis of patients with PD comorbidity and to differentiate vulnerability per PD Cluster. Method: 309 out-patients with remitted recurrent MDD (SCID-I; $HDRS_{17} \leq 10$) were included within two comparable RCTs and were assessed at baseline with the Personality Diagnostic Questionnaire-4+ (PDQ-4+), the Dysfunctional Attitude Scale Version-A (DAS-A), the Leiden Index of Depression Sensitivity (LEIDS), the Ruminative Response Scale (RRS), and the Inventory of Depressive Symptomatology-Self Report ($IDS\text{-}SR_{30}$). Results: We found an indication that the PD prevalence was 49.5% in this remitted recurrently depressed sample. Having a PD (and higher levels of personality pathology) was associated with dysfunctional beliefs, cognitive reactivity, and rumination. Extreme 'black and white thinking' on the DAS was not associated with personality pathology. Brooding was only associated with a Cluster C classification ($t(308)=4.03$, $p<.001$) and with avoidant PD specifically ($t(308)=4.82$, $p<.001$), while surprisingly not with obsessive compulsive PD. Discussion: The current study was the first to examine cognitive vulnerability including cognitive reactivity and rumination in patients with PDs, and demonstrated that, even after controlling for depressive symptomatology, dysfunctional beliefs, cognitive reactivity, and rumination were associated with personality pathology. Rumination could be a pathway to relapse for patients with Avoidant PD, although this has to be examined. Replication of our findings concerning cognitive vulnerability and specific PDs is necessary.

Submitted as: van Rijsbergen, G.D.[a], Kok, G.D.[a], Elgersma, H.J., Hollon, S.D., Bockting, C.L.H. Personality and Cognitive Vulnerability in Remitted Recurrently Depressed Patients. [a] Shared first authorship.

Introduction

A consistent finding among patients with Major Depressive Disorder (MDD) is the high prevalence of personality disorders (PDs). Depending on the instrument used, prevalence rates of PD comorbidity during MDD typically range between 40-80 % (M. Fava et al., 2002; Fournier et al., 2008; Hirschfeld, 1999; Shea, Pilkonis, Beckham, & Collins, 1990). Few studies examined PD comorbidity prevalence after remission from MDD. Comorbid PD diagnoses appear to be low to moderately stable, and fluctuations over time have been suggested to represent the disorder itself, rather than a mood state effect of MDD (Costa, Bagby, Herbst, & McCrae, 2005; Grilo et al., 2004; Lopez-Castroman et al., 2012; Morey et al., 2010; Shea et al., 2002). However, it has been demonstrated that personality pathology is generally more stable when measured dimensionally (i.e., continuous levels of pathology; Durbin & Klein, 2006; Melartin, Haukka, Rytsälä, Jylhä, & Isometsä, 2010; Samuel et al., 2011). There is ample evidence that having a comorbid PD is a negative prognostic factor for the course of MDD, which is reflected by a longer time to remission and increased risk of relapse up to six years after remission (Grilo et al., 2010; Newton-Howes et al., 2006; Skodol et al., 2011). MDD with PD comorbidity (i.e., higher scores on dimensional pathology measures) more than tripled the 10-year risk of mortality and suicide (Hansen, Wang, Stage, & Kragh-Sorensen, 2003), whereas the presence of a borderline PD was related to multiple instead of single suicide attempts over 10 years (Boisseau et al., 2012). Therefore, it is highly relevant to study whether modifiable cognitive vulnerability is associated with comorbid PDs, and might therefore contribute to a poor prognosis.

Within the cognitive model, rigid latent dysfunctional beliefs (i.e., attitudes, schemas) are a potential cognitive vulnerability factor for relapse. However, according to the cognitive model, these latent beliefs have to be activated by schema-matching life events to play a role in the onset, persistence and relapse of MDD (Beck, 1967). Although several studies supported the notion that patients with higher dysfunctional beliefs are at increased risk of relapse (Bockting, Spinhoven, Koeter, Wouters, & Schene, 2006; Jarrett et al., 2012; Lewinsohn et al., 1999; Otto et al., 2007; ten Doesschate et al., 2010), the predictive validity of schemas for the first onset of

depression and the general role of schema-matching life events is less well validated (Charlton & Power, 1995; Parker, Gladstone, Mitchell, Wilhelm, & Roy, 2000). Patients with comorbid PDs generally endorse heightened levels of dysfunctional beliefs even in the absence of depression, which is most pronounced in Cluster C (Farabaugh et al., 2007; Ilardi & Craighead, 1999). However, the finding that dysfunctional beliefs do not predict relapse above the PD itself has resulted in the suggestion that this phenomenon is merely a reflection of the overlap between dysfunctional beliefs and personality pathology (Craighead, Sheets, Craighead, & Madsen, 2011; Otto et al., 2007). Rather than dysfunctional belief content, it might be the extremity of the belief (i.e., response style) that renders patients with comorbid PD vulnerable for a chronic recurrent course of MDD. A 'black and white' dichotomous thinking style has been related to relapse in depression in some studies (Peterson et al., 2007; Teasdale et al., 2001), and could be especially prominent in patients with a Cluster B (e.g., borderline PD) diagnosis. Whereas some studies find supportive evidence for the presence of extreme 'black and white' thinking in borderline PD (Arntz & ten Haaf, 2012; Veen & Arntz, 2000), this is not always corroborated (Sieswerda, Barnow, Verheul, & Arntz, 2013).

Building on the cognitive model (Beck, 1967), Teasdale (1988) suggested that dysfunctional beliefs can also be activated by mild dysphoric mood in the remitted phase instead of matching life events (i.e., cognitive reactivity) to serve as a vulnerability factor for relapse in depression. Although the activation of dysfunctional beliefs by means of mood-induction has been frequently examined (e.g. Segal et al., 2006; van Rijsbergen et al., 2013), it appears that cognitive reactivity can also be assessed using a self-report measure that instructs patients to recall how they responded during periods of mild dysphoric mood (i.e., Leiden Index of Depression Sensitivity, van der Does, 2002). Ilardi (1999) noted that patients with PDs are characterized by inner chronic distress, potentially serving as a natural primer to activate latent dysfunctional beliefs (i.e., cognitive reactivity). In line with this reasoning, one might expect cognitive reactivity after remission to be more strongly related to PDs than dysfunctional beliefs.

Alternatively, responding to dysphoric mood with a maladaptive repetitive focus on the causes, meaning and consequences of depressive symptoms (i.e., rumination;

Nolen-Hoeksema, 1991) makes patients vulnerable for early relapse as well (Michalak, Hölz, & Teismann, 2011; Nolen-Hoeksema, 2000). Especially the brooding component was related to the emergence of depressive symptoms (Treynor, Gonzalez, & Nolen-Hoeksema, 2003). In patients with acute MDD, rumination was associated with borderline PD features, but not with any specific PD (n = 257) (Abela, Payne, & Moussaly, 2003; Watkins, 2009). The same was found in student samples without MDD (Baer & Sauer, 2011; Smith, Grandin, Alloy, & Abramson, 2006), although in these student samples obsessive compulsive PD features were also related to rumination (Smith et al., 2006). To our knowledge, no studies to date examined rumination in patients remitted from MDD with comorbid PDs.

The current study is the first to examine a combination of potentially modifiable cognitive vulnerability (i.e., dysfunctional beliefs, extremity of beliefs, cognitive reactivity, and rumination) in remitted patients with comorbid personality pathology (categorical as well as dimensional). The results might aid in tailoring specific interventions for this high risk group. We will examine cross-sectional associations between cognitive vulnerability and PD comorbidity. We expected that the presence of comorbid PDs and higher levels of personality pathology (i.e., continuous) would be associated with all measured cognitive vulnerability (i.e., dysfunctional beliefs, cognitive reactivity and extremity) and rumination, and, due to the nature of the sample (i.e., remitted patients) more strongly to cognitive reactivity than to dysfunctional beliefs. When studying the classification of specific clusters, we expected dysfunctional beliefs to be related to all clusters (in line with Ilardi & Craighead, 1999). Given the mixed results for the association of specific PD clusters with extreme thinking, and the absence of studies on cognitive reactivity and rumination, we explored their associations with specific PD clusters. Finally, we examined cognitive vulnerability in the three most prevalent PDs in the current sample in an exploratory fashion.

Method

This study combines the baseline data of two randomized controlled trials; for readability referred to as Study A and Study B. Study A focused on Preventive Cognitive Therapy (PCT) in groups as an addition or alternative to antidepressant medication (ADM) versus ADM alone in the prevention of relapse in recurrent depression (Bockting et al., 2011) whereas Study B studied an Internet adaptation of PCT added to Treatment-As-Usual (TAU) versus TAU alone in the prevention of relapse in recurrent depression (Bockting, Kok et al., 2011). Both protocols were approved by the Medical Ethical Committee for Mental Health Institutions (METiGG) and all patients provided written informed consent prior to participation.

Participants

In both studies, patients were included who had a) experienced at least two lifetime Major Depressive Episodes (MDEs), of which the last MDE was no longer than two years ago; b) current remission of the last MDE for at least two months, both defined according to the Diagnostic and Statistical Manual of Mental Disorders (DSM–IV) and assessed with the Structured Clinical Interview for DSM–IV disorders (SCID-I) (First et al., 2001) administered by trained interviewers; and c) a current score of ≤ 10 on the 17-item Hamilton Depression Rating Scale ($HRSD_{17}$) (Hamilton, 1960). Exclusion criteria were: current mania, hypomania, a history of bipolar illness, any psychotic disorder (current and previous), organic brain damage, current alcohol or drug abuse, predominant anxiety disorder, and recent electroconvulsive therapy. Both studies included remitted patients, but differed to the extent that Study A only included patients who a) were currently on ADM for at least six months, and b) did not receive psychotherapy more frequent than twice per month. In Study B, there were no restrictions with respect to both type and frequency of current care (i.e., psychotherapy, ADM, specialty care, no care).

Measures

Following inclusion, prior to receiving PCT, patients completed online questionnaires including:

Dysfunctional Attitude Scale – version A (DAS-A)

In the current study the Dutch adaptation of the DAS-A (Douma, 1991; A. N. Weissman, 1979) was used to assess rigid dysfunctional beliefs. On the DAS-A patients rated their agreement with all 40-items on a seven-point scale that ranged from 'totally agree' to 'totally disagree'. The total number of extreme responses on the DAS was used as a measure of extreme response style on the DAS. The DAS-A demonstrated excellent reliability in a previous study (α = .86; Dozois, Covin, & Brinker, 2003), and had a reliability of α = .93 in the current study.

Leiden Index of Depression Sensitivity (LEIDS)

The LEIDS is a self-report questionnaire that aims to measure cognitive reactivity to sad mood independent of mood induction (van der Does, 2002). After imagining a mildly depressed mood, patients rated all 34-items on a scale that ranged from one 'not applicable' to five 'strongly applicable'. An exemplary item is 'When I feel sad, I feel I can afford less mistakes'. The LEIDS was found to be significantly associated (r = 0.43) with changes in dysfunctional beliefs following mood induction (van der Does, 2002). Cronbach's alpha in the current study was .87.

Ruminative Response Scale (RRS)

Rumination was assessed using the validated Dutch adaptation of the RRS, the RRS-NL (Raes & Hermans, 2007). Patients rated their agreement on a scale that ranged from 'almost always' to 'almost never'. The five-item subscale brooding was used, as this aspect of rumination appears to specifically reflect dysfunctional and maladaptive thinking and is strongly related to depression later in time (Treynor et al., 2003). In the current study, Cronbach's alpha for the total RRS was .94, and .64 for the brooding subscale.

Personality Diagnostic Questionnaire 4+ (PDQ-4+)

The PDQ-4+ (Hyler, 1994) is a self-report personality questionnaire with 99 true/false items that directly correspond to personality disorders in the DSM-IV (American Psychiatric Association, 2000). Moreover, the total PDQ-4+ score reflects overall continuous personality pathology. The psychometric properties of the PDQ-4+ appear to be reasonable, with adequate internal consistency in a recent study (between 0.49 and 0.75; (Hopwood, Thomas, Markon, Wright, & Krueger, 2012). Lower internal consistencies of the PDQ-4+ have been attributed to the nature of PDs itself (Carr & Francis, 2010; McHoskey, 2001). A known limitation of the PDQ is its risk of false positives (Hyler, Skodol, Kellman, Oldham, & Rosnick, 1990). To further improve diagnostic accuracy, the threshold of diagnosing a personality disorder was increased by raising the number of criteria required for each disorder by one, which increased diagnostic power and higher agreement between the PDQ-4+ and the SCID-II in a previous study (van Velzen, Luteijn, Scholing, van Hout, & Emmelkamp, 1999).

Inventory of Depressive Symptomatology – Self Report (IDS-SR)

The Dutch translation of the 30-item IDS-SR (Rush et al., 1996) was used to assess levels of depressive symptomatology. The IDS-SR_{30} is a self-report measure on which patients rate their symptoms on a scale of zero to three. The IDS-SR_{30} rates all DSM-IV core symptom domains including mood, cognitive and psychomotor symptoms, but also commonly associated symptoms including anxiety. The IDS-SR_{30} has excellent internal consistency ($\alpha = 0.92$) (Rush et al., 2003).

Data analysis

In order to combine the baseline data from both studies, we first assessed potential differences between patient groups. Groups were compared on gender, age, age of onset, number of previous MDEs, last MDE severity, percentage of ADM use as well as clinical measures including HDRS17, DAS, LEIDS, RRS, PDQ-4+ (both continuous and categorical) and IDS-SR_{30}.

Subsequently, multiple imputation with 40 imputations was used to account for the 8.8 % of the data that were missing. Multiple imputation is a state-of-the art technique,

and preferred above other missing data approaches including case-wise deletion (Schafer & Graham, 2002).

As suggested, the threshold for PDQ-4+ personality disorder diagnosis was increased by one criterion for each disorder (van Velzen et al., 1999). We then used univariate regression analysis to examine the association of personality (both continuous pathology and presence versus absence of a diagnosis) on the following dependent measures: dysfunctional beliefs, cognitive reactivity, and rumination (brooding). We also examined whether personality pathology was related to an extreme response style on the DAS-A. Because the number of extreme responses showed strong deviations from a normal distribution, we used the non-parametric Mann Whitney U test instead. Moreover, we studied whether the presence versus absence of personality Clusters (A, B or C) was specifically related to any of the dependent measures. Finally, we analyzed cognitive vulnerability in the three most prevalent PDs. In all models we checked whether residual depressive symptomatology changed the effect of personality pathology on the dependent variable by adding the IDS-SR_{30} as a covariate in the analysis.

Results

Preliminary analyses

In order to analyze the data of the two trials together, we first assessed differences between the two studies. Patients did not differ between trials with respect to gender, age, age of onset, number of previous MDEs, $HDRS_{17}$ at inclusion, receiving current psychotherapy, personality disorders (continuous pathology, absence versus presence of a disorder, absence versus presence of a cluster, total number of disorders), dysfunctional beliefs (including extreme responses; DAS), cognitive reactivity, brooding, and residual symptoms (IDS-SR_{30}) (all *p's* > .05). Therefore, the baseline data of both trials was merged. However, as expected, current use of ADM was higher in Study A than in Study B (100 % versus 51 %, χ^2 (1, N = 307) = 80.380, $p < .001$). Moreover, last depressive episode severity was somewhat higher in Study A than in Study B (Mann

Whitney U = 8619.5; z = -3.38; *p* = .001; 36 % severe versus 22 % severe). Controlling for ADM use and last episode severity did not change any of the results.

Patients

In total 309 patients were included in both trials. Patients were predominantly female (68.6 %) and were currently in remission as defined by the $HDRS_{17}$ (M = 3.6, SD = 2.8) with a median of 4 previous MDEs (IQR = 3.0). Table 1 presents the demographic and clinical characteristics of the complete sample.

Table 1. Baseline demographic and clinical characteristics (N = 309)

Characteristic	n	Descriptive
Female (%)	309	68.6
Age	309	46.6 (10.6)
Married or cohabiting (%)	308	59.5
Patients on antidepressants (%)	307	68.6
Current psychotherapy (%)	255	55.5
Median previous MDEs (IQR)	309	4.0 (3.0)
Age of first onset	301	29.1 (12.7)
Severity last episode [a]	308	
Minor (%)		20.8
Moderate (%)		51.9
Severe (%)		27.3
Inclusion HDRS17	309	3.6 (2.8)
Dysfunctional beliefs (DAS-A)	281	130.6 (31.2)
Extremity of dysfunctional beliefs (DAS-A)	281	5.7 (5.8)
Cognitive reactivity (LEIDS)	274	105.0 (16.0)
Brooding (RRS)	275	11.2 (2.8)
Depressive symptomatology ($IDS\text{-}SR_{30}$)	294	17.5 (10.7)
Continuous PD score (PDQ-4+)	283	24.2 (12.5)
Number of PDs (PDQ-4+)	283	1.1 (1.5)

Note, Descriptive characteristics represent mean ± SD unless stated otherwise. IQR = Interquartile Range, PD = Personality Disorder. [a]Last episode severity is based on the number of SCID-I depression symptoms (5 symptoms corresponds to minor, 6-7 symptoms corresponds to moderate, whereas 8-9 symptoms corresponds to severe depression).

Personality disorder prevalence

We found an indication that 49.5% of the patients in our sample had a comorbid personality disorder. Of all patients 22.3 % had one PD, 14.5 % had two PDs and 12.7 % had three or more PDs. Most patients had a diagnosis in Cluster C (39.6 %) followed by Cluster A (16.6%) and Cluster B (8.1%). Avoidant PD was the most prevalent disorder (29.7 %), followed by obsessive compulsive PD (19.8 %), and then paranoid PD (9.2 %).

Vulnerability for continuous and categorical personality pathology

As depicted in Table 2, both PD diagnosis and continuous pathology were significantly related to dysfunctional beliefs, cognitive reactivity and brooding. Continuous PD pathology accounted for 40 % of variation in dysfunctional beliefs. The results did not change significantly when we controlled for residual depressive symptoms (see Supplemental Table 1). Patients with a comorbid PD did not differ significantly from patients without comorbid PD on their level of extreme responses on the DAS-A (Mann Whitney U = 11770.25, z = - .18, *p* = .86).

Table 2. Univariate regression models of the presence of a PD and continuous personality pathology on the cognitive measures (n = 309)

Dependent variable	B	SE (B)	R2	T	*p*	FMI
DAS – A						
PD	27.02	3.23	.19	8.37	< .001	.06
Continuous PD	1.50	.11	.40	13.42	< .001	.16
LEIDS						
PD	10.09	1.71	.11	5.90	< .001	.06
Continuous PD	.52	.07	.19	7.7	< .001	.18
Brooding						
PD	1.24	.35	.05	3.54	< .001	.20
Continuous PD	.07	.02	.09	4.38	< .001	.38

Note, FMI = Fraction Missing Information, DAS-A = Dysfunctional Attitude Scale Version A, LEIDS = Leiden Index of Depression Sensitivity.

Vulnerability by personality cluster

As depicted in Table 3, dysfunctional beliefs were significantly associated with the presence of a Cluster A (t (308) = 6.45, $p < .001$), Cluster B (t (308) = 6.07, $p < .001$) and Cluster C diagnosis (t (308) = 8.24, $p < .001$). The same was true for cognitive reactivity; Cluster A (t (308) = 3.41, $p = .001$), Cluster B (t (308) = 3.07, $p = .002$) and Cluster C (t (308) = 5.66, $p < .001$). Most of the variance in both dysfunctional beliefs and cognitive reactivity was accounted for by having a Cluster C diagnosis, remarkably more variance was explained in dysfunctional beliefs ($R^2 = .19$) than in cognitive reactivity ($R^2 = .10$). Only having a Cluster C diagnosis was significantly related to brooding scores (t (308) = 4.03, $p < .001$).

However, after controlling for residual symptoms, the presence of a PD diagnosis in Cluster A was no longer related to cognitive reactivity (t (308) = 1.72, $p = .086$). No other effects of controlling for residual symptoms were found (see Supplemental Table 2).

Finally, non-parametric tests revealed that there were no differences in extremity of thinking on the DAS-A between the presence versus absence of a PD diagnosis in Cluster A, Cluster B and/or Cluster C (all p's > .10).

Table 3. Univariate regression models of the presence of the PD clusters on the cognitive measures (n = 309)

Dependent variable	B	SE (B)	R2	T	*p*	FMI
DAS - A						
Cluster A	28.16	4.37	.12	6.45	< .001	.06
Cluster B	34.48	5.68	.12	6.07	< .001	.17
Cluster C	27.26	3.31	.19	8.24	< .001	.07
LEIDS						
Cluster A	8.15	2.39	.04	3.41	.001	.13
Cluster B	9.69	3.16	.04	3.07	.002	.25
Cluster C	9.90	1.75	.10	5.66	< .001	.06
Brooding						
Cluster A	.66	.47	.01	1.42	.155	.21
Cluster B	1.08	.63	.01	1.70	.090	.37
Cluster C	1.37	.34	.06	4.03	< .001	.13

Note, FMI = Fraction Missing Information, DAS-A = Dysfunctional Attitude Scale Version A, LEIDS = Leiden Index of Depression Sensitivity.

Vulnerability in the three most prevalent personality disorders

Finally, we assessed cognitive vulnerability in the three most prevalent PDs in the current sample, being: Avoidant PD (n = 84), obsessive compulsive PD (n = 56), and paranoid PD (n = 26). Together, these three disorders comprised 72 % of the total number of PDs diagnosed (231 diagnoses in total).

Being diagnosed with an avoidant PD was significantly associated with dysfunctional beliefs (t (308) = 8.10, $p < .001$), reactivity of these beliefs (t (308) = 5.73, $p < .001$), as well as brooding (t (308) = 4.82, $p < .001$). Similarly, paranoid PD was associated with dysfunctional beliefs (t (308) = 6.33, $p < .001$), but also reactivity of these beliefs (t (308) = 2.91, $p = .004$). Although brooding was unrelated to having a Cluster A diagnosis in general, having a paranoid PD (Cluster A) was associated with brooding levels (t (308) = 2.13, $p = .034$). Remarkably, having an obsessive compulsive PD was unrelated to brooding (t (308) = 1.61, $p = .11$), although the effect was in the

right direction. Having an obsessive compulsive PD was associated with higher levels of dysfunctional beliefs (t (308) = 5.30, $p < .001$) and cognitive reactivity (t (308) = 3.18, $p = .002$). After correcting for residual symptoms with the IDS-SR_{30}, having a paranoid PD was no longer related to brooding (t (308) = 1.57, $p = .11$) and cognitive reactivity (t (308) = 1.70, $p = .09$). No other effects of controlling for residual symptoms were found.

Discussion

The central aim of the current study was to examine potentially modifiable cognitive vulnerability factors (i.e., dysfunctional beliefs, extremity of beliefs, cognitive reactivity, and rumination) in patients remitted from MDD with and without a comorbid PD, in order to unravel why these patients might be prone to a chronic and persistent course of MDD (Grilo et al., 2010; Skodol et al., 2011), and to be able to specifically tailor interventions for this patient group. Our findings indicate that PDs after remission from recurrent MDD seem highly prevalent (49.5% prevalence). This closely resembles findings by previous studies that reported a 48% (Personality Assessment Form; recurrent MDD sample; (Pilkonis & Frank, 1988), 50% (SCID-II; primarily recurrent MDD sample; Farabaugh et al., 2007), and 51.9% (SCID-II; primarily non-recurrent MDD sample; Sato et al., 1994). PD prevalence after remission, as well as a study during the acute-phase of MDD that asked patients to recall their typical self (Fournier et al., 2008). In line with Farabaugh et al. (2007), avoidant PD, obsessive compulsive PD, and paranoid PD were the most prevalent PDs in our remitted population.

We found that rumination was associated with both the presence of a PD and higher levels of PD pathology. A closer inspection revealed that rumination was associated with avoidant PD and not to obsessive compulsive PD (although the effect was in the right direction), as was also found in a student sample (Smith et al., 2006). Rumination might serve as a way of avoiding both cognitive and active problem solving, since it was found that rumination and avoidance (behavioral as well as cognitive and experiential) are associated (Cribb, Moulds, & Carter, 2006; Moulds, Kandris, Starr, & Wong, 2007). As rumination has also been linked to borderline PD dimensions in several previous studies (Smith et al., 2006; Watkins, 2009), we examined post-hoc

whether this was also applicable to borderline PD in our patient group. Similar to paranoid PD, we found that borderline PD was related to rumination, however not over and above residual depressive symptomatology. This suggests that in these patients, rumination might be a reflection of depressive symptomatology instead of the PD itself. Since we assessed cluster classification in an exploratory fashion, future studies should attempt to replicate these findings. Moreover, since effective relapse prevention interventions are available (Guidi et al., 2011; Vittengl et al., 2007), it is worthwhile to examine whether these interventions target rumination specifically.

As far as we know, this was the first study that examined cognitive reactivity in remitted patients with and without a PD. According to Beck's cognitive model applied to personality disorders (Beck & Freeman, 1990; Pretzer & Beck, 1996) and suggested by previous studies (Craighead et al., 2011; Ilardi & Craighead, 1999), we expected dysfunctional beliefs to be more easily activated in patients with PD comorbidity. We indeed found that cognitive reactivity was associated with both having a PD or higher levels of PD pathology, which suggests that PD pathology might serve as an innate primer or stressor for dysfunctional beliefs. Cognitive reactivity was associated with classification in all three PD Clusters, although the association with Cluster A disappeared after controlling for residual depressive symptoms.

Similar to our cognitive reactivity findings, and replicating previous studies (Farabaugh et al., 2007; Ilardi & Craighead, 1999), we also found that dysfunctional beliefs appear to represent an overarching cognitive vulnerability for all PD clusters. However, remarkable for a remitted population, dysfunctional beliefs showed a stronger association with PD levels (40% explained variance) than cognitive reactivity (19% explained variance). Even after controlling for residual symptomatology in our analyses, the association with dysfunctional beliefs remained the strongest. This could imply that, due to the innate stress caused by the PD, the DAS itself is also a measure of cognitive reactivity in this group. Given the moderate association between the LEIDS and depressive symptomatology (r = .30, p < .001), comparable to the DAS, the LEIDS appears to be affected by state effects of depression as well. Finally, we found that a dichotomous thinking style (i.e., rigid 'black and white thinking') was not specifically related to PDs or levels of PD pathology in our remitted patient group. Findings on the

role of dichotomous thinking in PDs and borderline PD specifically (in the absence of MDD) have been mixed (Arntz & ten Haaf, 2012; Sieswerda et al., 2013; Veen & Arntz, 2000). A recent study demonstrated that instead of dichotomous thinking; negativistic thinking (i.e., general more negative evaluations of others) was typical for borderline PD (Sieswerda et al., 2013).

The cognitive model is not explicit about how and when early critical life events lead to an accumulation and consolidation of dysfunctional beliefs into MDD, PD or their combination (Beck & Freeman, 1990; Pretzer & Beck, 1996). It still has to be determined whether dysfunctional beliefs accumulate over time and consolidate into a PD, or whether they are a byproduct of the PD itself. The lack of differentiation in the associations of dysfunctional beliefs and cognitive reactivity with the PD clusters strongly suggests that this cognitive vulnerability might be an epiphenomenon of the PD (Craighead et al., 2011; Otto et al., 2007). Despite similar patterns, the low to moderate association (r = .44; p < .001) between dysfunctional beliefs (DAS) and their reactivity (LEIDS) does suggest that these questionnaires measure different constructs.

Strengths of the current study include use of a large recurrently depressed patient sample (N = 309), relatively unaffected by state effects (i.e., depressive symptomatology) due to remission of the MDE, the use of several well-validated measures, and the examination of a combination of cognitive vulnerability including rumination on the level of both PD clusters and disorders. Several limitations should also be taken into account. First of all, we used a self-report instrument to diagnose PDs (i.e., the PDQ-4+) instead of the Semi-structured Interview for Personality Disorders (SCID-II). Although we adjusted the PDQ-4+ with one criterion to reduce over-diagnosis and, moreover, the prevalence of PDs in the current sample was comparable to other studies using remitted MDD samples (Farabaugh et al., 2007; Pilkonis & Frank, 1988; Sato et al., 1994), we cannot completely rule out that the PDQ-4+ overestimated the prevalence of PDs. Additionally, due to the low prevalence of some of the PDs (i.e., antisocial PD, n = 1; histrionic PD, n = 4; and narcissistic PD, n = 4), we were not able to examine cognitive vulnerability in these PDs specifically. Since all patients were in remission, the relations with cognitive indices we found might be an underestimation as patients with for example chronic episodes were not included in our trial. Moreover, the

current study used a cross-sectional approach to study vulnerability in patients with a comorbid PD. Therefore, we were unable to determine whether these cognitive vulnerabilities indeed predict a poor MDD prognosis (i.e., faster, more severe or persistent relapse) in these patients prospectively. Finally, the inclusion criteria of our studies (i.e., highly recurrent group, absence of predominant anxiety disorder, between age of 18-65 years, fluent in Dutch,) might affect the generalizability of the results.

Future studies should attempt to replicate our findings on cognitive vulnerability and specific PDs. Since dysfunctional beliefs were more strongly associated with PDs after remission than cognitive reactivity, the question arises whether the assessment of mood-linked activation of dysfunctional beliefs is relevant in this specific group. Future studies should also examine whether rumination and other modifiable cognitive vulnerability mediate the effects that PDs have on time to relapse, in order to be able to better understand the mechanisms that drive relapse prevention strategies. Subsequently tailoring preventive interventions (i.e., specifically targeting rumination in Cluster C PD patients) might improve their efficacy.

Supplemental Tables

Supplemental Table 1. Multivariate regression models of the presence of a either PD and continuous personality pathology on the cognitive measures with the IDS-SR_{30} in the first step (N = 309)

Dependent variable	B	SE (B)	t	*p*	R^2 change	FMI
DAS – A						
Step 1						
IDS-SR_{30}	1.18	.15	8.00	< .001	.18	.07
Step 2						
PD	19.53	3.43	5.70	< .001	.09	.08
Step 2						
Continuous PD	1.35	.13	10.13	<.001	.23	.16
LEIDS						
Step 1						
IDS-SR_{30}	.41	.08	5.04	<.001	.09	.14
Step 2						
PD	7.63	1.88	4.06	< .001	.05	.09
Step 2						
Continuous PD	.47	.08	5.72	<.001	.11	.22
Brooding						
Step 1						
IDS-SR_{30}	.04	.02	2.12	.034	.02	.27
Step 2						
PD	1.10	.39	2.81	.005	.03	.29
Step 2						
Continuous PD	.07	.02	3.68	< .001	.07	.45

Note, FMI = Fraction Missing Information, IDS-SR_{30} = Inventory of Depressive Symptomatology Self-Report, DAS-A = Dysfunctional Attitude Scale Version-A, LEIDS = Leiden Index of Depression Sensitivity.

Supplemental Table 2. Multivariate regression models of PD cluster classification on the cognitive measures with the IDS-SR_{30} in the first step (N = 309)

Dependent variable	B	SE (B)	t	*p*	R^2 change	FMI
DAS - A						
Step 1						
IDS-SR_{30}	1.18	.15	8.00	< .001	.18	.07
Step 2						
Cluster A	28.12	4.58	3.96	< .001	.05	.13
Step 2						
Cluster B	25.70	5.70	4.51	< .001	.05	.24
Step 2						
Cluster C	21.10	3.30	6.39	< .001	.10	.09
LEIDS						
Step 1						
IDS-SR_{30}	.41	.08	5.04	<.001	.09	.14
Step 2						
Cluster A	4.38	2.55	1.72	.086	.01	.17
Step 2						
Cluster B	6.49	3.21	2.02	.044	.02	.28
Step 2						
Cluster C	7.80	1.79	4.37	< .001	.06	.05
Brooding						
Step 1						
IDS-SR_{30}	.04	.02	2.12	.034	.02	.27
Step 2						
Cluster A	.33	.51	0.66	.511	<.01	.26
Step 2						
Cluster B	.81	.66	1.24	.218	.01	.38
Step 2						
Cluster C	1.24	.36	3.46	.001	.04	.14

Note, FMI = Fraction Missing Information, IDS-SR_{30} = Inventory of Depressive Symptomatology Self-Report, DAS-A = Dysfunctional Attitude Scale Version-A, LEIDS = Leiden Index of Depression Sensitivity.

Chapter 6

Effectiveness of psychological interventions in preventing recurrence

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Abstract

Depressive disorder is highly recurrent and a large part of its disease burden stems from these recurrences. The aim of this review was to meta-analytically examine the effectiveness of preventive psychological interventions with the aim to reduce the risk of recurrence versus treatment-as-usual and versus antidepressant medication. Based on specific criteria, we identified and evaluated 24 randomized controlled prevention studies and conducted a meta-analysis. The random-effects model was used to compute the pooled relative risk of recurrence (RR). Findings indicated that preventive psychological interventions were superior to treatment-as-usual (RR=0.64, 95%CI=0.53-0.76, z= 4.89, p<0.001, NNT=5) and to antidepressants (RR=0.81, 95%CI=0.69-0.96, z=2.50, p=0.013, NNT=12). Meta-regression showed homogeneity in effect size across a range of study, population and intervention characteristics, though some heterogeneity could be explained by whether or not there was an intervention in the acute phase (p=0.006). We conclude that there is converging evidence that preventive psychological interventions help to reduce the risk of relapse and recurrence in depressive disorder.

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Introduction

Major depressive disorder (MDD) affects 16% of the population on a lifetime basis (R. C. Kessler, Chiu, Demler, Merikangas, & Walters, 2005). Of all people with MDD, at least 45% experience recurrent depressive disorder with seven to eight depressive episodes over the course of their life (Kruijshaar et al., 2005) and spending as much as 21% of their lifetime in a depressed condition (Vos et al., 2004). MDD is therefore perhaps best described as a largely chronically recurrent disorder with much of its disease burden stemming from its recurrent nature (Judd, 1997).

Our aim is to meta-analytically evaluate the randomized trial literature of psychological interventions aiming to prevent recurrence. The reviewed interventions are cognitive (behavior) therapy (CT), mindfulness-based cognitive therapy (MCT), interpersonal therapy (IPT), problem-solving therapy (PST) and psychodynamic-/psychoanalytic therapy (PDT). The comparator conditions are either treatment-as-usual (TAU) or use of antidepressant medication (ADM). We hypothesized that the psychological interventions are superior to treatment-as-usual and outperform pharmaceutical interventions in the continuation or maintenance phase.

Methods

Primary studies

We included studies in the meta-analysis when the following criteria were met: a) a randomized controlled trial b) that examined adult patients in the age bracket of 18-64 year c) with recurrent MDD d) who were in remission at randomization e) in which the effect (recurrence) of a psychological intervention was measured f) offered in the continuation or maintenance phase g) with the aim of reducing the risk of recurrence and h) with a comparison to a control condition. Control conditions could be classed as treatment-as-usual (TAU; routine clinical management, assessments only, no treatment, waiting-list control with unrestricted access to TAU) or use of antidepressant medication (ADM). We included only English-language articles.

Psychological interventions could be classed as ‘cognitive (behavior) therapy’ (CT), ‘mindfulness-based cognitive therapy’ (MCT), ‘interpersonal therapy’ (IPT), problem-solving therapy (PST) and psychodynamic- (psychoanalytic) therapy (PDT). CT is based on the cognitive theory that negative automatic thoughts, maladaptive information processing, and avoidance behavior play a key role in the development and maintenance of depression (Beck, Rush, Shaw, & Emery, 1979). MCT is a protocol-led, group-based skills training program designed to teach recovered depressed patients how to disengage from automatic, cognitive processing patterns linked to relapse (Segal, Williams, & Teasdale, 2002). IPT originates from interpersonal theory (Klerman et al., 1987). It links stressful life events and insufficient social support to the development and maintenance of depressive symptoms (M. M. Weissman, Markowitz, & Klerman, 2007). PST is a brief treatment focused on the building of practical problem-solving skills. The goal is to stimulate an active attitude towards everyday problems and, hereby, to achieve a reduction in mental health problems (Hawton, Salkovskis, Kirk, & Clark, 1989). PDT is a manual-based approach focusing on the affective, behavioral and cognitive aspects of relationships from a psychodynamic point of view (De Jonghe, Rijnierse, & Janssen, 1994; De Jonghe, 2013). It comprises intervention methods such as clarification, interpretation and confrontation (each addressing the topics of intrapsychic conflict and resistance) and focuses on relationships and emotions (Watzke, Rueddel, Koch, Rudolph, & Schulz, 2008).

Finally, each study had to report recurrence rates using established screeners with a pre-defined cut-off point for MDD, such as the Hamilton Rating Scale of Depression (HRSD) (Hamilton, 1960) and Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), or a diagnostic interview such as the Structured Clinical Interview for DSM-IV Axis 1 Disorders (SCID-I) (First et al., 2001). Definitions of relapse and recurrence were not used in a consistent manner throughout the reviewed studies. As a consequence, we could not draw a meaningful distinction between remission and recovery (henceforth ‘recovery’), relapse and recurrence (henceforth ‘recurrence’), and continuation and maintenance treatment (henceforth ‘maintenance’).

We excluded studies that reported on long-term effects of acute-phase therapies because the evaluation of the prophylactic effects of acute episode treatment is a

different approach altogether. Neither did we include studies focussing on a direct comparison of preventive interventions. Studies that were mainly focused on psychiatric disorders other than recurrent MDD or somatic disorders were also excluded.

Central clinical end-term

The central clinical outcome was the recurrence rate of MDD as defined by study investigators (i.e. crossing the cut-off on a depression rating scale or a change in diagnostic depression status based on clinical assessment). Outcomes were evaluated at the longest available follow-up.

Search methods for identification of studies

A first literature search was conducted in September 2012 and an updated and expanded search was conducted in August 2013. Free text and MeSH terms were used for searches in Medline, PsycInfo, CINAHL, Embase and the Cochrane database. The studies had to be published in English, Dutch or German. Keyword searches were conducted by combining the following main terms: cognitive, cognitive behavior therapy, mindfulness, mindfulness-based cognitive therapy, interpersonal therapy, problem-solving, problem-solving therapy, psychodynamic, psychodynamic therapy, psychoanalytic, psychoanalytic therapy, continuation, maintenance, relapse, recurrence, prevention, therapy, treatment, recurrent, recurrence, depressive disorder and depression. Additional delimiters were adults and randomized controlled trials. To supplement the searches of published research, the Internet was also utilized to locate additional studies.

Data collection and analysis

Selection of trials

Included and excluded studies were collected following the Preferred Reporting Items for Systematic reviews and Meta-Analyses, PRISMA (Moher, Liberati, Tetzlaff, & Altman, 2010). The first selection was the responsibility of the first author (KBL) and was made using the title, abstract and keywords whereby the full-text article was

retrieved when in doubt. All authors of significant papers in the research field were contacted and asked to complete the list of selected publications. Two independent researchers (KBL and GK) carried out the final selection. Any disagreement was resolved by consensus.

Assessment of risk of bias in included studies

Flaws in the design, conduct, analysis, and reporting of randomized trials can cause the effect of an intervention to be underestimated or overestimated. The Cochrane risk-of-bias method (Higgins & Green, 2008) was applied for assessing risk of bias to make the process clearer and more accurate. This method consists of six items. Two items assess the strength of the randomization process in preventing selection bias in the assignment of participants to interventions: adequacy of sequence generation and allocation concealment. The third item (masking) assesses the influence of performance bias on the study results. The fourth item assesses the likelihood of incomplete outcome data, which raises the possibility of bias in effect estimates. The fifth item assesses selective reporting, the tendency to preferentially report statistically significant outcomes. This item requires a comparison of published data with trial protocols, when such are available. The final item refers to other sources of bias that are relevant in certain circumstances such as sponsorship bias.

Data extraction

We collated an evidence table in which extracted data of each study were recorded. Two reviewers (KBL and GK) extracted the data independently and resolved disagreement by consensus. Extracted data included; mean age, number of previous episodes, percentage females, type of intervention in acute phase (in both active and control arm), type of intervention in maintenance phase (in both active and control arm), duration of intervention in the maintenance phase, length of follow-up, setting (community, primary care, secondary care), number of patients per study-arm, definition of recurrence and recurrence rates per study arm.

Data analysis

The central clinical end-term in this meta-analysis was the reduction in the recurrence rate in the intervention group as compared with the comparator condition. This gave rise to the effect size called relative risk (RR). A RR below 1 indicates that the intervention is superior to the comparator condition, because fewer recurrences occurred.

The meta-analysis was based on DerSimonian and Laird's random-effects model (DerSimonian & Laird, 1986), because heterogeneity was likely to be substantial in the context of various intervention modalities and comparator conditions, while follow-up measurements ranged from 17-332 weeks. An α-level of 0.05 (2-tailed) was used for hypothesis testing. In addition to the RR, the risk-difference (RD) was calculated and transformed by inversion into the number-needed-to-treat (NNT).

Heterogeneity was evaluated using the I^2 statistic (Higgins & Thompson, 2002) and can be interpreted as the percentage of between-study variance that cannot be explained by the random sample error of the primary studies. As a rule, heterogeneity is deemed low, moderate or high when I^2 is 25%, 50% or 75%, respectively. The 95% confidence-interval of I^2 was estimated using STATA's downloadable 'heterogi'-procedure.

Publication bias was assessed using the funnel plot. The presence of publication bias was further evaluated using Duval and Tweedie's Trim & Fill procedure (Duval & Tweedie, 2000). Essentially, this procedure re-estimates the meta-analytically pooled effect size after considering publication bias by imputing missing studies. The bias can then be observed as the difference between the unadjusted pooled effect size and the adjusted one. We also computed the fail-safe *N* for the pooled RR as another way to gauge the robustness of the pooled RR in the possible presence of publication bias.

The correlation between the effect size of the interventions and the characteristics of the primary studies was explored using meta-regression. In meta-regression, the effect size (RR) of each the primary studies is regressed on the characteristics of the studies, the study population and the intervention. The meta-analytic regression model contained seven predictor variables: proportion female, mean age, number of previous episodes, (type of intervention) in the acute phase, duration of preventive intervention,

duration of follow-up and setting where participants were recruited. The meta-analytic dataset was analyzed with help of Comprehensive Meta-Analysis (CMA, Version 2.2.057, 2010) (2012, http://www.meta-analysis.com). Stata (StataCorp, Version 8.2, 2009) was used for carrying out the multivariate meta-regression and calculating the 95% confidence intervals of the I^2-statistic.

All findings were summarized in a table according to the methodology described by the GRADE working group (Guyatt et al., 2008).

Results

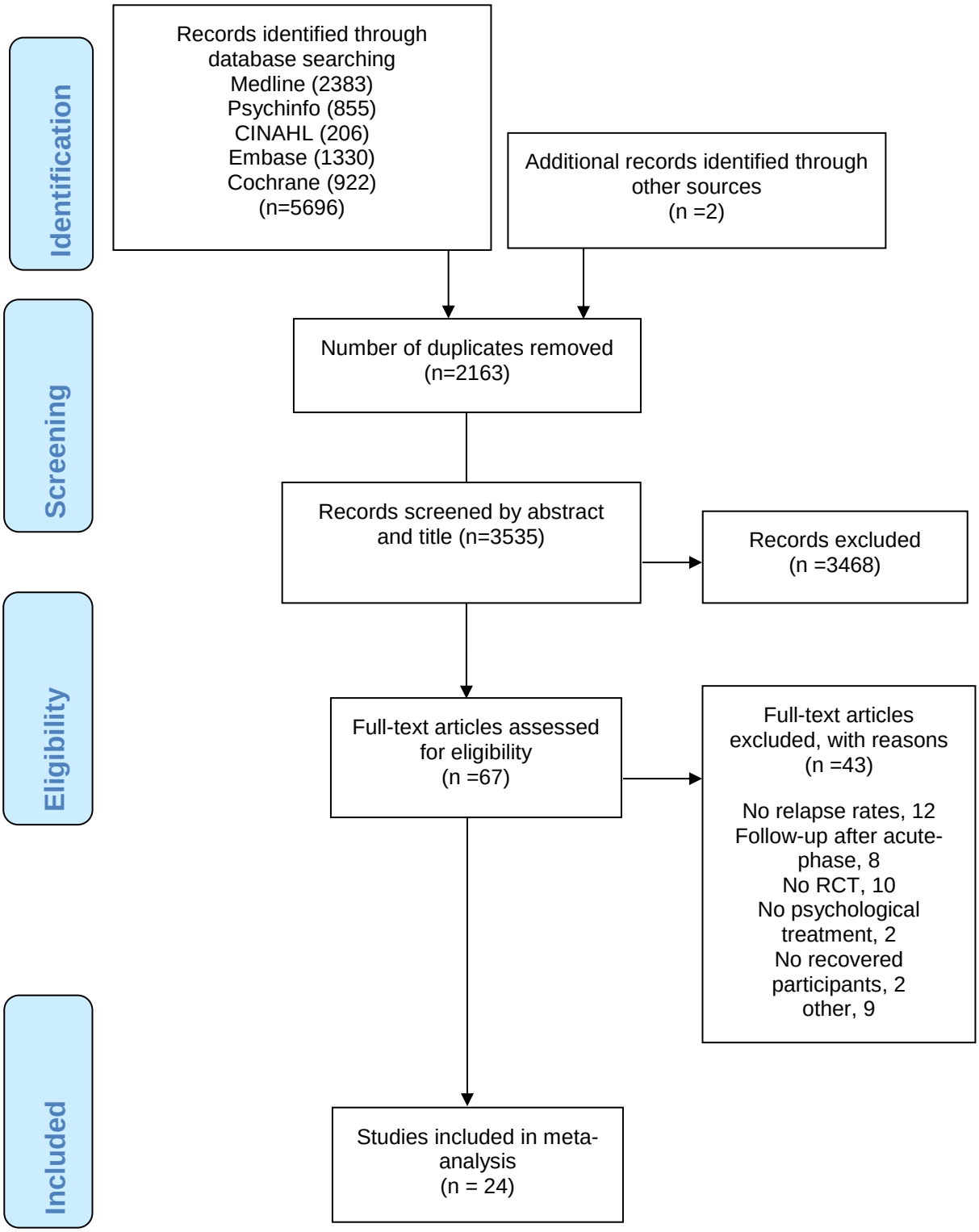
Description of included studies

Having examined a total of 3,335 abstracts, we retrieved 67 full text papers. Of these, 43 studies were excluded because they did not meet the inclusion criteria. The remaining 24 studies met all inclusion criteria. Five trials compared 3 conditions, thus testing multiple contrasts. As a result, this meta-analysis was based on 24 studies and 29 contrasts. Figure 1 depicts the flow chart of the selection process.

No trials evaluating PST or PDT met the inclusion criteria. Fifteen trials (16 contrasts) evaluated preventive CT, 3 trials (6 contrasts) evaluated IPT, and 6 trials (7 contrasts) evaluated MCT. Twelve contrasts compared a psychological intervention with ADM and 17 compared a psychological intervention with TAU. Fourteen studies were conducted in Europe, 9 in the United States and 1 in Australia. Duration of follow-up ranged between 17 weeks and more than 6 years (332 weeks).

CT as maintenance therapy was delivered through various modes; weekly group sessions, individual sessions, through the Internet and as booster sessions (various number of sessions during various duration of periods with a minimum of 3 sessions). All trials evaluating MCT consisted of two-hour weekly sessions over 8 consecutive weeks, eventually followed by a few booster sessions. IPT was delivered in individual sessions (varying from monthly maintenance sessions over 8 months to weekly maintenance sessions over 4 months).

Figure 1. Flow chart of the literature search



The 24 primary studies encompassed 2,002 patients in total. In 20 contrasts the patients had been recipients of a preceding acute-phase therapy during the trial, which was either medication or cognitive therapy or a combination of both. At randomization, all patients were depression free (residual symptoms were allowed), but ‘at risk’ of a recurrence into yet another episode of MDD. A total of 907 patients were randomized to an intervention condition: 504 received preventive CT, 142 IPT and 261 MCT. The remaining 1,095 patients were randomized to comparator conditions: 425 receiving ADM and 670 receiving TAU.

Mean age was 42.3 years, mean percentage of female participants was 72.4% and the mean number of previous episodes was 4.1. Selected characteristics are presented in Table 1.

Table 1. Selected characteristics of 24 included studies[a]

Author	Intervention AP [b]	Comparator AP [b]	Intervention MP	Comparator MP	FU (wks)	Definition recurrence	Setting	Intervention MP (wks)	RR intervention MP	RR comparator
Baker et al, 1998	Group CBT	Group CBT	CBT	TAU	22	BDI=17	Community	12	6/10	7/9
Blackburn et al, 1998	CT	ADM	CT	ADM	104	HRSD=8 and BDI=9 or retreatment	Primary and secondary care	26	3/13	7/9
Blackburn et al, 1997	CT	ADM	CT	ADM	52	HRSD=14	Secondary care	104	4/17	4/13
Bockting et al, 2009	n/a	n/a	CT + TAU	TAU	286	MDE according to SCID	Community, primary and secondary care	8	69/88	73/84
Bondolfi et al, 2010	n/a	n/a	MBCT + TAU	TAU	60	MDE according to SCID	Community, primary and secondary care	8	9/27	10/28
Conradi et al, 2007	n/a	n/a	CBT	TAU	156	MDE (CIDI)	Primary care	156	21/38	39/62
Fava et al, 1998	ADM	ADM	CT	TAU	332	MDE (RDC defined)	Secondary care	20	10/20	15/20
Fava et al, 2002	ADM	ADM	CT + ADM	ADM	60	MDE (RDC defined)	Secondary care	6	¼	4/4
Fava et al, 2004	ADM	ADM	CT	TAU	332	MDE (RDC defined)	Secondary care	20	8/20	18/20
Frank et al, 1990a	ADM + IPT	ADM + IPT	IPT	TAU	156	MDE (RDC defined) + HRSD=15 + Raskin=7	Unknown	156	1/26	1/23
Frank et al, 1990b	ADM + IPT	ADM + IPT	IPT	ADM	156	MDE (RDC defined) + HRSD=15 + Raskin=7	Unknown	156	1/26	0/28
Godfrin et al, 2001	n/a	n/a	MCT + TAU	TAU	56	MDE according to DSM-IV	Secondary care	8	12/40	32/47
Hollandäre et al, 2011	n/a	n/a	CBT (Internet)	TAU	26	MDD according to SCID	Community	10	4/38	14/37

Author	Intervention AP[b]	Comparator AP [b]	Intervention MP	Comparator MP	FU (wks)	Definition recurrence	Setting	Intervention MP (wks)	RR intervention MP	RR comparator
Hollon et al, 2005	CT	ADM	CT	ADM	104	MDE or HRSD=14,≥ 2 wks	Secondary care	52	5/20	7/14
Jarret et al, 2000a	CT	TAU	CT	TAU	104	MDE (RDC defined) or retreatment	Secondary care	10	3/7	6/7
Jarret et al, 2000b	CT	ADM	CT	ADM	104	MDE (RDC defined) or retreatment	Secondary care	10	3/7	4/7
Jarret et al, 2001	CT	CT	CT	TAU	104	MDE (RDC defined)	Community, primary and secondary care	36	15/41	22/43
Klein et al, 2004	CBASP (CBT)	CBASP (CBT)	CBASP (CBT)	TAU	52	MDD and HRSD=16 for 2 visits	Secondary care	52	1/42	8/40
Klerman et al, 1974a	ADM	ADM	IPT	TAU	35	Not clear	Secondary care	36	4/25	9/25
Klerman et al, 1974b	ADM	ADM	IPT	ADM	35	Not clear	Secondary care	36	4/25	3/25
Kuyken et al, 2008	n/a	n/a	MCT + TAU	ADM	65	MDE according to SCID	Primary care	52	29/61	37/62
Ma et al, 2004	n/a	n/a	MCT + TAU	TAU	60	MDE (DSM-IV defined)	Primary care and community	36	14/36	23/37
Paykel et al, 2005	n/a	n/a	CBT +ADM	ADM	275	MDD > 4 wks or HAMD=13≥ 8 wks	Secondary care	32	48/80	51/78
Perlis et al, 2002	ADM	ADM	CT + ADM	ADM	28	MDE at any visit, HRSD = 15 at 2 consecutive visits	Secondary care	26	4/66	5/66

Table 1. Selected characteristics of 24 included studies[a]

Author	Intervention AP [b]	Comparator AP [b]	Intervention MP	Comparator MP	FU (wks)	Definition recurrence	Setting	Intervention MP (wks)	RR intervention MP	RR comparator
Schulberg et al, 1996a	IPT	TAU	IPT	TAU	17	Symptomatic (HRSD=13)	Primary care	18	17/91	44/92
Schulberg et al, 1996 b	IPT	ADM	IPT	ADM	17	Symptomatic (HRSD=13)	Primary care	18	17/91	23/91
Segal et al, 2010a	ADM	ADM	MCT	TAU	78	HRSD=16 2 consecutive weeks + MDE on SCID	Community, primary and secondary care	8	10/26	18/30
Segal et al, 2010b	ADM	ADM	MCT	AD,	78	HRSD=16 2 consecutive weeks + MDE on SCID	Community, primary and secondary care	8	10/26	13/28
Teasdale et al, 2000	n/a	n/a/	MCT + TAU	TAU	60	Recovery or remission, HRSD-17 < 10	Community, primary and secondary care	26	31/71	38/66

Note, [a]Abbreviations used in Table 1: ADM, anti-depressant medication; FU=Follow-up; AP, acute phase; BDI, Beck Depression Inventory (Beck et al., 1961); TAU, treatment-as-usual; CBASP; 'Cognitive Behavioral Analysis System of Psychotherapy'; C(B)T, Cognitive (Behavior) Therapy; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-IV; HRSD, Hamilton Rating Scale for Depression(Hamilton, 1960); IPT, Interpersonal Therapy; MCT, Mindfulness Based Cognitive Therapy; MDD, Major Depressive Disorder; MDE, Major Depressive Episode; MP, maintenance phase; Raskin, Raskin Depression Rating Scale (Raskin, Schulterbrandt, Reatig, & McKeon, 1969); RCT, randomized controlled trial; RDC, Research Diagnostic Criteria; SCID, Structured Clinical Interview for Depression (First et al., 2001); wks, weeks.b An intervention in the acute phase as part of this specific RCT; RR, Risk Rate.

Psychological interventions versus treatment-as-usual

Pooled RR

Here we restrict attention to the comparison of psychological interventions versus TAU. It was hypothesized that psychological interventions (of any kind) would be superior to TAU. We obtained seventeen randomized trials that compared a psychological intervention with TAU. The pooled relative risk was 0.64 (95% CI 0.53-0.76) and statistically significant (z= 4.89, p<0.001), indicating that psychological interventions were more successful in decreasing the risk of recurrence than TAU (Table 2, Figure 2). The mean follow-up time was somewhat longer than two years (114 weeks).

Pooled RD and NNT

The risk-difference was 0.19 (95% CI 0.125-0.255), corresponding to a number-needed-to-treat (NNT) of 5.3. In other words, it takes 5 patients to be treated with a psychological intervention (CT, MCT or IPT) rather than TAU to prevent one recurrence.

Heterogeneity

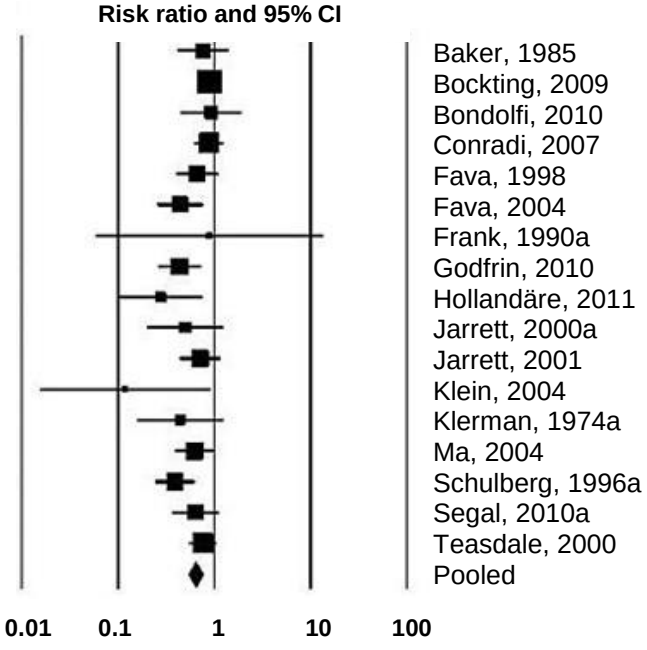
The test of heterogeneity indicated that the observed variability in effect sizes across the studies was greater than that expected to occur by chance alone (χ^2 =32.41, df=16, p=0.009).

The corresponding I^2 was 51% (95% CI 14-72%) corresponding with moderate heterogeneity (Higgins et al., 2003).

Table 2. Risk ratios and 95% confidence-intervals for psychological interventions versus treatment as usual

Study name	Statistics for each study				
	Risk ratio	Lower limit	Upper limit	z-value	p-value
Baker, 1985	0.771	0.417	1.427	-0.827	0.408
Bockting, 2009	0.902	0.786	1.035	-1.466	0.143
Bondolfi, 2010	0.933	0.450	1.935	-0.185	0.853
Conradi, 2007	0.879	0.623	1.239	-0.738	0.461
Fava, 1998	0.667	0.402	1.106	-1.570	0.116
Fava, 2004	0.444	0.255	0.775	-2.857	0.004
Frank, 1990a	0.885	0.059	13.354	-0.089	0.929
Godfrin, 2010	0.441	0.264	0.735	-3.136	0.002
Hollandäre, 2011	0.278	0.101	0.767	-2.471	0.013
Jarrett, 2000a	0.500	0.202	1.239	-1.497	0.134
Jarrett, 2001	0.715	0.435	1.176	-1.321	0.187
Klein, 2004	0.119	0.016	0.909	-2.052	0.040
Klerman, 1974a	0.444	0.157	1.256	-1.529	0.126
Ma, 2004	0.626	0.687	1.012	-1.913	0.056
Schulberg, 1996a	0.391	0.242	0.631	-3.848	0.000
Segal, 2010a	0.641	0.364	1.130	-1.537	0.124
Teasdale, 2000	0.758	0.542	1.061	-1.615	0.106
Pooled	0.638	0.533	0.764	-4.887	0.000

Figure 2. Forest plot of risk ratios and 95% confidence-intervals for psychological interventions versus treatment-as-usual [a]



Note, [a] *Abbreviations used*: CI, confidence interval; a, study contrast versus treatment-as-usual.

Meta-regression

A meta-regression analysis was used to explore the heterogeneity in the effects across the studies in terms of sample characteristics (mean age, gender, number of previous depressive episodes and number of previous episodes), and the study's methodological characteristics (intervention in the acute phase, mean follow-up duration and setting). Whether or not there was an intervention in the acute phase (CT, MCT, IPT, ADM or combination versus none) helped partially explain heterogeneity across outcomes (b=-1.613, SEb=0.588, z=-2.74, p =0.006). Other sources of heterogeneity (e.g. variability in intervention and comorbidity) may also have contributed to the heterogeneity but were insufficiently reported to be included in the meta-regression.

Publication bias

Visual inspection of the funnel plot suggested that publication bias was likely in this meta-analysis of psychological interventions versus TAU. This impression was confirmed by the Egger test (intercept=-1.65, SE=0.41, p <0.001). Accordingly, Duvall and Tweedie's adjusted estimate was RR=0.82 (95% CI 0.68-0.99) and was based on eight additionally imputed studies. The adjusted estimate differed somewhat from the original (unadjusted) estimate of RR=0.64 (95% CI 0.53-0.76): the 95% confidence intervals have a considerable overlap, but the point estimates of RR fall outside the alternative intervals. That said, the conclusion that psychological interventions are statistically superior to TAU remained unaffected (Egger, Davey Smith, Schneider, & Minder, 1997; Rothstein, Sutton, & Borenstein, 2005). The robustness of the findings was further supported by a fail-safe N of 197, meaning that 197 undetected studies with no effect (RR=1) need to be included in the meta-analysis before the meta-analysis would cease to be statistically significant at p <0.05 (2-tailed).

Psychological interventions versus antidepressants

Twelve studies compared psychological interventions with ADM (Table 3, Figure 3). The pooled effect size was RR=0.81 (95% CI 0.69-0.96), which was statistically significant (z=2.50, p=0.013). No evidence was obtained for heterogeneity (χ^2= 8.57, df=11, p=0.662, I^2= 0%, 95% CI 0-58), although the 95% CI of the I^2 leaves room for

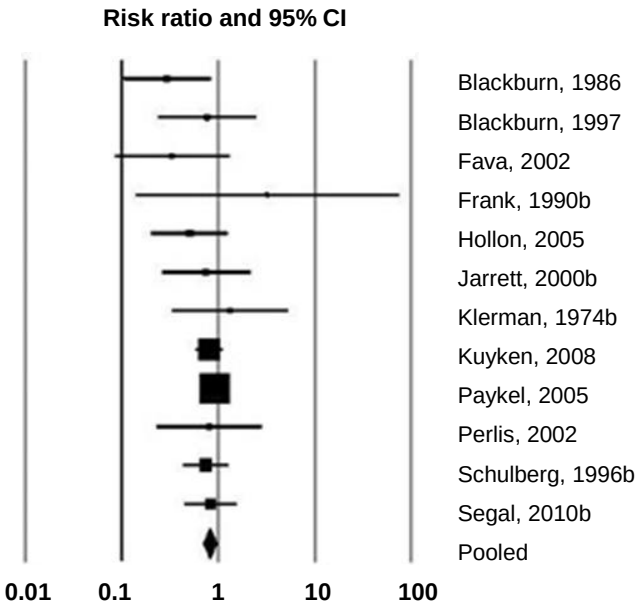
other interpretations. The mean follow-up period was somewhat less than two years (90 weeks). The risk-difference was 0.082 (95% CI 0.040-0.002) and the corresponding NNT was 12.2, demonstrating that 12 patients would need to be treated with a preventive psychological intervention rather than ADM to prevent a recurrence.

Visual inspection of the funnel plot did not suggest publication bias. Indeed, Egger test and Duvall and Tweedie's Trim & Fill showed no trend (Egger test intercept=-0.52, SE=0.41, *p*=0.23, Duvall and Tweedie's adjusted RR=0.85, 95% CI 0.70-1.04, based on three imputed studies).

Table 3. Risk ratios and 95% confidence-intervals for psychological interventions versus antidepressant medication

Study name	Statistics for each study				
	Risk ratio	Lower limit	Upper limit	z-value	p-value
Blackburn, 1986	0.297	0.104	0.850	-2.263	0.024
Blackburn, 1997	0.765	0.234	2.496	-0.444	0.657
Fava, 2002	0.333	0.085	1.312	-1.571	0.116
Frank, 1990b	3.222	0.137	75.752	0.726	0.468
Hollon, 2005	0.500	0.199	1.258	-1.473	0.141
Jarrett, 2000b	0.750	0.527	2.185	-0.527	0.598
Klerman, 1974b	1.333	0.332	5.356	0.405	0.685
Kuyken, 2008	0.797	0.571	1.112	-1.335	0.182
Paykel, 2005	0.917	0.721	1.168	-0.699	0.485
Perlis, 2002	0.800	0.225	2.848	-0.344	0.731
Schulberg, 1996b	0.739	0.424	1.288	-1.067	0.286
Segal, 2010b	0.828	0.442	1.553	-0.587	0.557
Pooled	0.812	0.690	0.956	-2.497	0.013

Figure 3. Forest plot of risk ratios and 95% confidence-intervals for psychological interventions versus antidepressant medication[a]



Note, [a]*Abbreviations used:* CI, confidence interval; b, study contrast versus antidepressant medication.

The effectiveness of different types of psychological interventions

Fifteen trials (16 contrasts) included CT, 3 trials included IPT (6 contrasts) and 6 trials (7 contrasts) included MCT (Table 4). The effect sizes of the different psychological interventions were roughly similar but -as expected- psychological interventions were more effective versus TAU than versus ADM.

Table 4. Risk ratios of different types of psychological interventions versus treatment-as-usual (TAU) and antidepressant medication (ADM) according to the random-effects model (DerSimonian and Laird) and fixed-effects model (Mantel-Haenszel)[a]

	Intervention	K	RR D-L	RR M-H (95% CI)	RD (95% CI)	I^2	Test of D-L	NNT
Versus TAU	All interventions	17	0.64 (0.53-0.76)	0.76 (0.69-0.83)	-0.190 (-0.255- -0.125)	51%	Z=4.89 *p*=0.000	5
	CT	9	0.68 (0.54-0.87)	0.82 (0.73-0.92)	-0.196 (-0.28- - 0.11)	52%	Z=3.12 *p* =0.002	5
	MCT	5	0.66 (0.53-0.82)	0.66 (0.53-0.82)	-0.205 (-0.32- - 0.09)	0%	Z=3.81 *p* =0.000	4
	IPT	3	0.41 (0.27-0.63)	0.41 (0.27-0.63)	-0.160 (-0.37- - 0.04)	0%	Z=4.10 *p* =0.000	6
Versus ADM	All interventions	12	0.81 (0.69-0.96)	0.81 (0.69-0.96)	-0.082 (-0.161- -0.004)	0%	Z=2.50 *p* =0.013	12
	CT	7	0.71 (0.51-0.99)	0.81 (0.66-1.01)	-0.19 (-0.35- - 0.03)	17%	Z=2.04 *p* =0.041	5
	MCT	2	0.80 (0.60-1.08)	0.80 (0.60-1.08)	-0.11 (-0.25-0.04)	0%	Z=1.46 *p* =0.146	9
	IPT	3	0.83 (0.50-1.38)	0.83 (0.50-1.38)	-0.002 (-0.068-0.073)	0%	Z=0.71 *p* =0.477	499

Note, [a]*Abbreviations used in Table 2*: ADM, anti-depressant medication; CT, Cognitive (Behavior) Therapy; CI, confidence interval; I^2, heterogeneity; IPT, Interpersonal Therapy; K, number of contrasts; MCT, Mindfulness-based Cognitive Therapy; NNT, number-needed-to-treat; RD, risk difference; RR D-L, random-effects according to DerSimonian and Laird; RR M-H, fixed-effects according to Mantel-Haenszel; TAU, treatment-as-usual.

Quality of included studies

We created GRADE profiles and classified the overall quality of the evidence (high, moderate, low) based on the GRADE system using 6 criteria (Guyatt et al., 2008); study design (all RCTs), study limitations, inconsistency, indirectness, imprecision and other bias (e.g. publication bias). Overall, the quality of the studies was low. We conducted a meta-regression to analyze whether the size of the effects (RR) systematically co-varied with study quality. This was not the case (b= 0.242, SEb=0.945, z=0.26, *p*=0.798).

Discussion

Main findings

We identified 24 randomized controlled trials in a total of 2,002 patients examining the effect of psychological interventions to prevent the onset of yet another episode in recurrent depression. We found randomized controlled prevention trials for cognitive (behavior) therapy, mindfulness-based cognitive therapy and interpersonal therapy, but no trials for problem-solving therapy or psychodynamic therapy. Meta-analysis of the available studies demonstrated that psychological interventions are effective in preventing recurrences in recurrent depression over a time-span of about two years versus treatment-as-usual and antidepressant medication with relative risks of 0.64 and 0.81, respectively. These effects were statistically significant. The effect sizes of the different psychological interventions were roughly similar. An unanticipated chance finding was that the effectiveness of preventive interventions was enhanced when the patient had received an intervention (treatment-as-usual, antidepressant medication or both) during the acute phase of the depression.

Limitations

We recognize a number of limitations in this meta-analysis. First, apart from differences in the methodological quality of the included trials that caused heterogeneity, there were additional differences between the primary studies with regard to the composition of the patient groups and type of interventions. For example, treatment-as-usual was often poorly described. These differences are likely to have caused some heterogeneity in the data, but owing to poor reporting could not be explored in a meta-regression. Second, the number of participants included in some studies was small, limiting the interpretation of the results. However, smaller studies are weighted less in a meta-analysis and have therefore a smaller impact on the results overall. Third, definitions of relapse and recurrence were inconsistent across the trials and the duration of depression-free periods also varied widely. Because of imprecise definitions and inconsistent terminology, we could not make a meaningful distinction between relapse and recurrence nor between continuation and maintenance treatment in this meta-analysis. This may have been another source of heterogeneity. For that reason we preferred to make use of the random effects model for meta-analysis and explored heterogeneity in a number of ways. These analyses attested to the robustness of the findings. Fourth, publication bias could not be ruled out in the meta-analysis of psychological interventions versus TAU and it is possible that unpublished trials showed null findings or even adverse outcomes. Fifth, it is unlikely that the number of previous depressive episodes have been reported reliably in the primary studies. The number of previous episodes is most likely underreported (Andrews, Poulton, & Skoog, 2005). The fact that we did not find an effect of number of previous episodes in our meta-analysis might be caused by a downward bias due to under-reporting. Sixth, this meta-analysis imposed a language restriction. Findings can only be generalized to North America, Australia and Northwest Europe because most studies were conducted in these regions. Seventh, network meta-analysis might have allowed for more sophisticated (indirect) comparisons between psychological treatments. However, this method was not used as we wanted to restrict the analyses to the direct (head-on) comparisons of psychological interventions versus ADM and TAU.

Despite these limitations, we found supporting evidence for the effectiveness of psychological interventions to prevent relapses and recurrences in remitted patients with a history of recurrent depressive disorder. Our finding that these interventions have greater efficacy than any comparator condition is consistent with results from Vittengl's (Vittengl, Clark, & Jarrett, 2009), Guidi's (Guidi et al., 2011) and Piet's (Piet & Hougaard, 2011) meta-analytic studies.

Implications

The public health significance of depressive disorders can be summed up in a small set of interrelated epidemiological parameters. Depression is a highly prevalent condition, affecting 16% of the population on a lifetime basis (R. C. Kessler et al., 2005). The mean duration of a depressive episode is about six months, but this varies considerably from one case to another (Kruijshaar et al., 2005). During the acute phase, depression has detrimental impacts on quality of life and is associated with excess mortality. Once present, depression often tends to run a recurrent course, characterized by multiple episodes over one's life course, typically amounting to seven or eight episodes, with each previous episode adding significantly to the risk of yet another recurrence. Patients experiencing recurrent MDD spent as much as 21% of their lifetime in a depressed condition (Vos et al., 2004). For these reasons, depression is associated with a substantial disease burden (Murray & Lopez, 1996) and substantial economic costs (Greenberg & Birnbaum, 2005; Smit et al., 2006).

Acute phase treatment of depression is the core business of psychiatry, but this approach is only partially successful in reducing the overall disease burden stemming from depression. As said, depression is characterized by a large number of patients experiencing multiple relapses and recurrences. This has important implications for the longer-term management of depression.

The National Institute for Health and Clinical Excellence (2010), pays specific attention to the continuation phase and prevention of relapse in its guidance on managing depression. Regarding the use of anti-depressants, NICE recommends to continue medication in ADM responders for at least 6 months after remission or even to continue for at least 2 years if there is a significant risk of relapse. The fact that some

recovered patients may not feel comfortable taking antidepressants for a long period, that they may feel dependent on them, and the often poor adherence and compliance rates in pharmaceutical intervention (ten Doesschate, Bockting, & Schene, 2009), are all factors contributing to the need of also offering psychological interventions as an alternative. This meta-analysis suggests that psychological interventions are even more effective in reducing the risk of recurrence than ADM.

Regarding psychological interventions, NICE recommends *individual CBT* for people who have relapsed despite antidepressant medication and for people with a significant history of depression and residual symptoms despite treatment or *MCT* for people who are currently recovered, but have experienced three or more previous episodes of depression. For all people with depression who are having individual CT for relapse prevention, the duration of treatment should typically be in the range of 16 to 20 sessions over 3 to 4 months. In 2012, the NICE guideline was updated with the specific note that further research is needed to determine the optimal treatment regimen.

In sum, psychological treatments can be seen as an effective and perhaps even attractive alternative, but the question how the optimal psychological treatment should ideally look like regarding length of treatment, number of sessions or delivery mode remains unanswered. Against a background of financial constraints in many health care systems, cost of treatment is of great concern. Cost-effective solutions demand an optimal balance between accessible, acceptable, effective and economically affordable treatments for the many patients suffering from recurrent depressions. Possible options have already been suggested, such as preventive interventions offered over the Internet (Holländare et al., 2011; Kelders, Pots, Oskam, Bohlmeijer, & van Gemert-Pijnen, 2013), by a nurse (Bosmans et al., 2012), by self-help (Biesheuvel-Leliefeld et al., 2012) or by low intensity psychological interventions (Rodgers et al., 2012). More trials focussing on the question how the ideal cost-effective psychological intervention offered in the continuation phase looks like, remain a necessity. Besides, more attention should be directed at problem-solving therapy and psychodynamic therapy as possibly valuable alternatives in the prevention of recurrent depression.

Lastly, this meta-analysis supports the use of psychological interventions in people who are at risk of relapse. Meta-regression showed that trials also offering an

intervention in the acute phase (ADM, psychological intervention or both) had a significant lower relapse rate than trials not offering an intervention in the acute phase. In other words, it might be important to look at depression as a series of disease-stages that need to be taken care of both during the acute-phase and also into the continuation and maintenance phase. Continuation treatment should then be embedded in an integrated way, seamlessly following up on the acute phase treatment.

Chapter 7

Mobile Cognitive Therapy trial design and protocol

Abstract

Background: Major depressive disorder (MDD) is projected to rank second on a list of 15 major diseases in terms of burden in 2030. The major contribution of MDD to disability and health care costs is largely due to its highly recurrent nature. Accordingly, efforts to reduce the disabling effects of this chronic condition should shift to preventing recurrence, especially in patients at high risk of recurrence. Given its high prevalence and the fact that interventions are necessary during the remitted phase, new approaches are needed to prevent relapse in depression. Method/design: The best established effective and available psychological intervention is cognitive therapy. However, it is costly and not available for most patients. Therefore, we will compare the effectiveness and cost-effectiveness of self-management supported by online CT accompanied by SMS based tele-monitoring of depressive symptomatology, i.e. Mobile Cognitive Therapy (Mobile CT) versus treatment as us usual (TAU). Remitted patients (n=268) with at least two previous depressive episodes will be recruited and randomized over (1) M- CT in addition to TAU versus (2) TAU alone, with follow-ups at 3, 12, and 24 months. Randomization will be stratified for number of previous episodes and type of treatment as usual. Primary outcome is time until relapse/recurrence over 24 months using DSM-IV-TR criteria as assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). For the economic evaluation the balance between costs and health outcomes will be compared across strategies using a societal perspective. Discussion: Internet-based interventions might be helpful in empowering patients to become their own disease managers in this lifelong recurrent disorder. This is, as far as we are aware of, the first study that examines the (cost) effectiveness of an E-mental health program using SMS monitoring of symptoms with therapist support to prevent relapse in remitted recurrently depressed patients.

Based on: Bockting, C.L.H., Kok, G.D., van der Kamp, L., Smit, F., van Valen, E., et al. (2011). Disrupting the rhythm of depression using Mobile Cognitive Therapy for recurrent depression: randomized controlled trial design and protocol. BMC Psychiatry, 11:12 doi:10.1186/1471-244X-11-12.

Introduction

Major depressive disorder (MDD) is projected to rank second on a list of 15 major diseases in terms of burden in 2030 (Mathers & Loncar, 2006). The contribution of MDD to disability and health care costs is largely due to its highly recurrent nature (Murray & Lopez, 1997; Vos et al., 2004). Accordingly, efforts to reduce the disabling effects of depression should shift to preventing recurrence, especially in patients at high risk of recurrence. Current maintenance therapy is often labour intensive involving collaboration among multiple health services over long periods. This is costly and prone to non-adherence to protocols on the part of health service providers and non-compliance on the part of patients. In this context it is essential to empower patients to become their own disease managers.

Cognitive therapy (CT) is an effective treatment of MDD and an effective preventive treatment (Beck, 2005; Bockting et al., 2005; Vittengl et al., 2007). In a multicenter RCT enrolling remitted recurrently depressed patients, we evaluated the efficacy and cost-effectiveness of a brief face-to-face CT added to treatment as usual (TAU) compared with TAU alone (Bockting et al., 2005). In line with other studies on CT, we found that CT was effective (and cost-effective) in preventing recurrences over a 2-year follow-up and even over 5.5 years, in patients with multiple previous episodes (Bockting et al., 2009).

Given its high prevalence and the fact that interventions are necessary during the remitted phase of this life-long disease, new approaches are needed to prevent relapse and recurrence in depression. This new approach must not only be acceptable to remitted patients, but also reach patients who often do not seek treatment in this phase of the disease. Several advantages have been noted of an e-mental health disease management program (Spek et al., 2007; Wright et al., 2005). First, SMS-based monitoring on depression makes it easier for the patient and therapist to detect relapse as early as possible. Second, Internet-based delivered cognitive therapy including SMS based monitoring by making use of cell phones (Mobile CT) is mainly a self-management intervention in which patients create their own prevention of relapse program. Third, patients can easily dose their own amount of online therapist support in

line with their needs. Overall, therapist's involvement may be reduced, as has been reported in the Internet-based treatment of acute depression (Wright et al., 2005). Finally, this self-management approach toward preventing relapse and recurrence in depression can be used at home or at any venue of convenience to the patient. A recent meta-analysis (Spek et al., 2007) revealed that Internet-based interventions seem to be effective interventions for acute depression, especially when the intervention is supported by therapist contact.

Trial objectives and Purpose

In this study, the addition of an Internet-based intervention with automated tele-monitoring (Mobile CT) to TAU, will be compared to TAU alone in a sample size of 214 (2x107) recovered patients. Alongside the randomized controlled trial, a cost effectiveness analysis (from a societal perspective) will be conducted.

It is hypothesized that adding Mobile CT is clinically superior to treatment-as-usual alone (TAU) for preventing relapse and recurrence in depressive disorder. In addition, we expect that the intervention dominates the comparator condition in terms of cost-effectiveness. Since comorbidity with concurrent chronic somatic illnesses, is defined by the American Psychiatric Association (2010) as a risk factor for future relapse and recurrence, differential response in this group of patients will be examined explicitly. We will also conduct moderator analysis to see if there are any baseline characteristics of the participants that are prognostically relevant for treatment response. Finally, we will conduct incremental cost-benefit regression analysis to identify subgroups where the intervention is particularly cost-effective.

Methods/Design

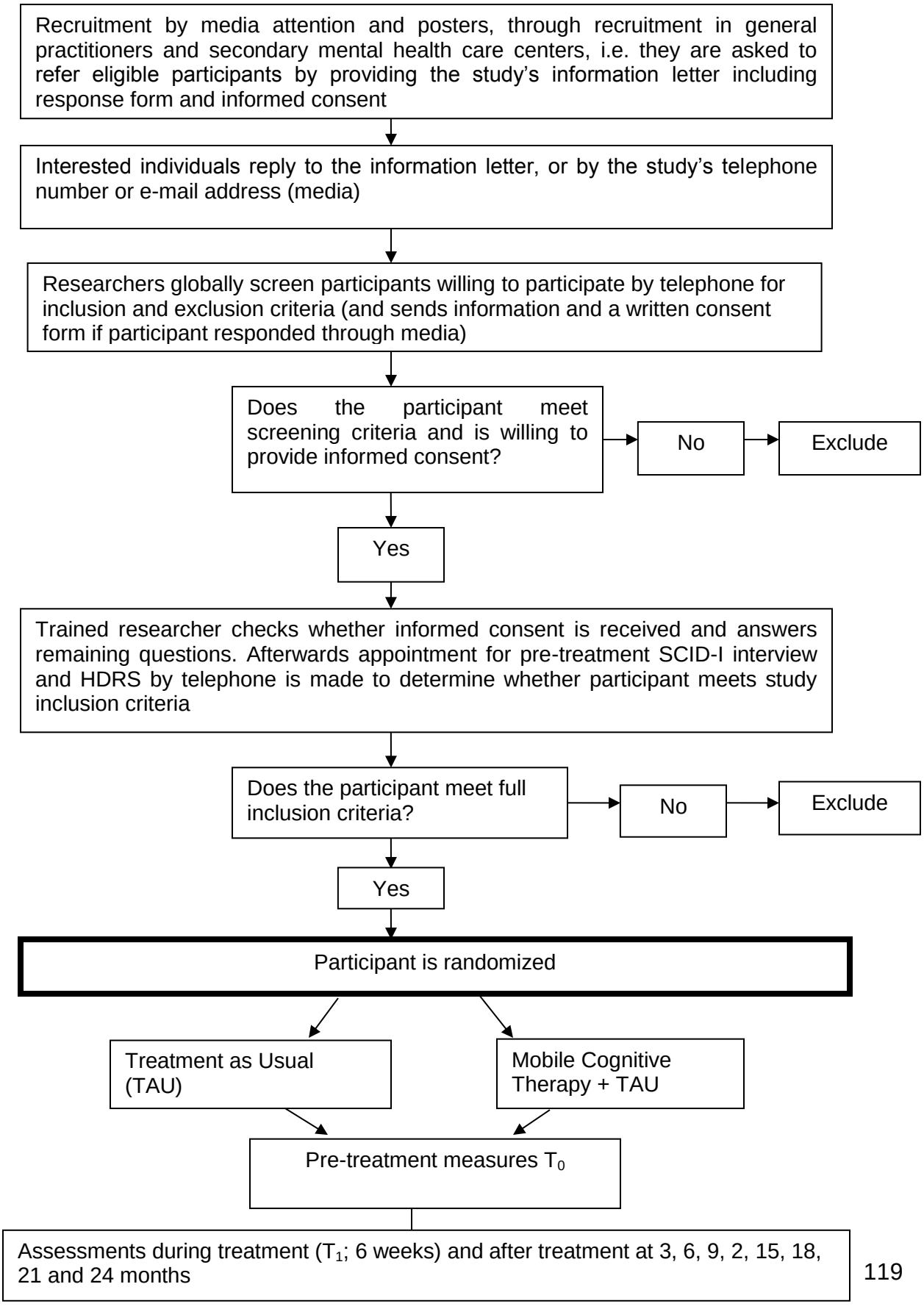
In this randomized controlled trial with a sample size of 268 participants (after accounting for 20% drop out, Mobile CT: 107, TAU: 107) we compare an Internet-supported self-directed prevention of relapse program as part of a SMS based monitoring versus treatment as usual (TAU). This Mobile CT program is called *Depression Free*. The target population is a group at elevated risk of relapse and

recurrence as identified in several guidelines (e.g. American Psychiatric Association, 2010; National Institute for Health & Care Excellence, 2010) that consumes a considerable amount of health care and for whom initial benefits of antidepressants (AD) may be wane off in the long run. Relapse rates rise with increasing numbers of previous episodes up to 70% in 5 years (Frank et al., 1990). In our previous study, we observed up to 62% recurrences within 2 years (Bockting, Spinhoven, Koeter, Wouters, & Schene, 2006).

Randomization will be undertaken by an independent researcher and will be stratified by the number of previous depressive episodes and type of care (i.e. care by a general practitioner versus care in a mental health center). Thereafter our researchers receive the participant number and the automatically random generated condition in the trial by email. For a Flow diagram of the assessment methods see Figure 1.

We monitor the primary outcome (relapse) over a period of 24 months. Assessments by trained assessors who are blind to treatment allocation (and whose blindness is checked within each assessment session) take place directly after the start of the treatment at three months, 12 and 24 months. For the research aims focused on potential working mechanisms of Mobile CT we added in between self-report assessments, i.e. baseline, 1.5 months and 3 months.

Figure 1. Flow Diagram



Interventions

Mobile CT-arm: This Mobile CT treatment builds on a previously evaluated face to face intervention, i.e. Preventive Cognitive Therapy (PCT) (Bockting, 2009) and has been developed in collaboration Bockting & van Valen (Bockting & van Valen, 2009) with the Trimbos Institute. The face to face PCT is an adapted type of cognitive therapy for acute depression (Beck et al., 1979) and specifically developed to prevent relapse in recurrent depression in remitted patients. It consists of eight sessions. Like in regular CT, each PCT session follows a fixed structure, with agenda setting, review of homework, explanation of rationale of each session, and assignment of homework. A manual describing the structure of the treatment and interventions used is available (Bockting, 2009). The intervention prevention program targets underlying cognitive vulnerability factors, such as depressogenic assumptions. Unlike CT for acutely depressed patients, PCT is not primarily directed toward modifying negative thoughts. Instead, it starts with the identification of negative thoughts and dysfunctional attitudes, aided by a self-report questionnaire with examples of attitudes and specific techniques such as the downward arrow technique. The focus of treatment is then directed on changing these attitudes using different cognitive techniques such as Socratic questioning and identification of positive attitudes. Moreover, patients are encouraged to practice with alternative attitudes in the final sessions. Remitted patients with a history of recurrences have an inability to retrieve specific memories from the past and this is associated with impaired problem-solving skills (e.g. Pollock & Williams, 2001), long-term course of depressive disorders (Petersen et al., 2004) and difficulties in recovering from depression. Part of the treatment is keeping a diary of positive experiences in order to enhance specific memories of positive experiences, instead of retaining overly general memories. Further specific relapse/recurrence prevention strategies are formulated in the last three sections of the Mobile CT resulting in a personal prevention plan.

The Mobile CT intervention is based on the above described face to face PCT. It is offered over the Internet in a series of 8 well-structured modules with online therapist contact (with a maximum of 4 telephone sessions) and by SMS. Each module includes assignments with automatically generated feedback. In addition, films can be activated

by the participant to explain more about specific topics. Each module can be completed in approximately 20 minutes, not counting the time required to complete additional assignments. If all assignments are completed, A personal prevention book will be automatically generated that can be of help in case of relapse of lowered mood. Automated checks will be conducted to ascertain that participants have not only completed modules, but also understood them correctly, before they can move on to the next. When participants do not log in on the intervention's website they will receive friendly reminders by SMS or mail to proceed with the intervention.

Depression-related outcomes (changes in mood) will be monitored with help of SMS (or by email if requested). To this end, participants periodically receive SMS messages in which they will be asked to rate their mood. Participants have to answer by sending a message back consisting of a number with which they rate their mood. When depressed mood is present and appears to persist, then the frequency of messages is increased and other depressive symptoms are monitored also using a web-based self-report assessment (IDS-SR_{30}) (Rush et al., 1996). In case there is indeed an indication for a depressive episode, participants will be interviewed using the Structural Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I) (First et al., 2001) and the Hamilton Rating Scale for Depression ($HRSD_{17}$) (Hamilton, 1960). This allows for the early detection of possible depression onset. In that scenario, participants receive advice and are encouraged to return to the website where they can find 'prescribed' modules. Hopefully, this offers them the opportunity to better cope with lowered moods.

The intervention is designed to be easily accessible, acceptable and as non-intrusive as possible, while at the same time allowing for tele-monitoring of health related outcomes over the time-span of several years. The web-based intervention has been developed by the Trimbos Institute, the University of Groningen, CrossOver Consultancy and their partners.

Treatment As Usual: The intervention will be compared to treatment as usual (TAU). In this context TAU is fairly heterogeneous: it typically consists of antidepressant (AD) maintenance medication in primary and secondary care, counseling or face-to-face PCT in secondary care, but often there is no treatment at all. To compare the intervention with TAU is relevant from a public health perspective: it would help to

demonstrate the intervention's added value over and above TAU. We will not intervene with TAU, but monitor TAU using a health service receipt interview, the TIC-P (Hakkaart-Van Roijen, 2002). We will assess compliance and adherence to AD use, but also the use of the Mobile CT program.

Sample size

With 107 in Mobile CT versus in TAU 107 participants per condition the trial will be powered to detect a difference of 20% in the cumulative incidence rate of relapse/recurrence with a 2 year follow-up in a 2-tailed test at the conventional alpha level of 0.05 and a power of (1-beta)=0.80, while conservatively assuming that relapse/recurrence will occur in 50% of the cases. Allowing for a drop-out of 20% we need to include 268 participants at baseline.

Referral and recruitment

Patients will be recruited by media (announcements, banners placed in various related websites, media attention in interviews), referral by general practitioners and mental health services. Patients with concurrent chronic somatic illnesses will be recruited by targeted marketing strategies (e.g. banners on website targeted on patients with chronic somatic illnesses, posters in hospitals) and specific recruitment at general practitioners.

Inclusion criteria

We include recovered patients with a history of at least two previous depressive episodes in the past five years. The last episode has to be at least 2 months and no longer than 2 years ago and a current score of ≤10 on the $HRSD_{17}$ (Hamilton, 1960) (in line with other prevention studies, e.g. Bockting et al., 2005; Vittengl et al., 2007). No restriction with respect to comorbidity on Axis II and III, i.e. a concurrent chronic somatic illness is defined as risk factor for relapse and recurrence, (American Psychiatric Association, 2010). Consenting participants need to be fluent in Dutch and have access to the Internet.

Exclusion criteria

Exclusion criteria are: current mania or hypomania or a history of bipolar illness, any psychotic disorder (current and previous), alcohol or drug misuse, predominant anxiety disorder.

Assessment of Eligibility and Baseline Measures

Informed consent

We inform patients about the study before they come into the study in two ways. First, by informing the patient through a therapist or a general practitioner (GP). If a therapist/GP wants to inform the patient himself, the patient then receives the information via the therapist/GP and is given a letter containing all the information. If the patient is interested in participating, then the participant will contact the researcher. Subsequently, the researcher checks that the participant understands all aspects of the trial. If the participant agrees to enter the trial, she completes a copy of the consent form and sends it to the researcher.

The second procedure we use is by directly informing the patient. Participants than initiate that contact with the researcher themselves (mostly informed by media/websites or by their former therapist/GP with a letter, by advertisements or interviews). Subsequently, the researcher informs the participant, the participant receives the information in a letter with all the information in it. If the participant is still interested in participating then the researcher checks that the participant understands all aspects of the trial. If they agree to enter the trial, they complete a copy of the consent form and send it to the researcher. We remind participants that they can withdraw from the trial at any time and that this has no consequences for their treatment as usual.

We ask consenting participants to provide information about their socio-demographic background and assess their eligibility in more detail using semi-structured clinical interviews (SCID-I, by telephone) and self-completed questionnaires (web-based). The researchers assess current and past diagnostic status using the SCID-I and $HRSD_{17}$. They ask participants to describe past and current treatments for

depression and use of antidepressants. If participants meet all inclusion and none of the exclusion criteria for the study, they enter the study.

Withdrawal

Participants can withdraw from treatment or from the study at any time.

Safety monitoring and reporting

The trial protocol has been approved by an independent medical ethics committee (METIGG). Eligible people will only be included as participants in the trial after informed consent has been obtained.

We record and report suspected serious adverse events to the Multi-center Ethic Committee (METIGG) according to their individual guidelines.

Baseline assessment

For the baseline assessment we ask participants themselves to complete the web-based self-report questionnaires in two packages, i.e. explicit and implicit measures. The first part with assessments starting directly within a week, the second part containing implicit measures will be offered within 2 days after completion of self-report assessments measures. The following self-report measures will be used: the Inventory of Depressive Symptomatology, IDS-SR_{30} (Rush et al., 1996), Nemesis Somatic illnesses list (R. de Graaf, Bijl, Ravelli, Smit, & Vollebergh, 2002), negative life events (Life events questionnaire, LGV) (Kraaij & de Wilde, 2001), self-esteem (Self-esteem Questionnaire) (Franck, De Raedt, Barbez, & Rosseel, 2008), personality pathology (Personality Diagnostic Questionnaire, PDQ-4) (Akkerhuis et al., 1996), everyday problems (EPCL) (Vingerhoets & van Tilburg, 1994), hypomania (HCL-32) (Angst et al., 2005), direct and indirect costs (TIC-P) (Hakkaart-Van Roijen, 2002) and Medication Adherence Questionnaire (MAQ) (Morisky, Green, & Levine, 1986), a measure of general quality of life (Euro-QOL EQ-5D) (EuroQol--a new facility for the measurement of health-related quality of life.1990) and rumination (Ruminative Responses Subscale of the Response Styles Questionnaire RSQ) (Treynor et al., 2003), dysfunctional attitudes (Dysfunctional Attitudes Scale, DAS) (A. N. Weissman, 1979), LEIDS (van der

Does, 2002), acceptance (Acceptance and Action Questionnaire, AAQ) (Hayes et al., 2004), coping (Utrecht Coping List, UCL) (Schreurs, van den Willige, Brosschot, Tellegen, & Graus, 1993), Mastery 7 (Pearlin & Schooler, 1978). After 6 weeks this set will be repeated with the exception of the TIC-P, LGV, PDQ, MAQ EQ-5D and Nemesis Somatic illnesses list. During follow-up every three months the following self-report assessments will be repeated: IDS-SR_{30}, HCL-32, TIC-P, EPCL, Mastery7 and EQ-5D will be administered. For a complete overview of the assessments see Table 1. Participants in the Mobile CT group will also answer questions of the Dutch version of the Credibility and expectancy questionnaire (E. L. de Graaf, Huibers, Riper, Gerhards, & Arntz, 2009; Devilly & Borkovec, 2000) before and after finishing Mobile CT.

Outcome measures

For an overview of the assessments at baseline, in between- and post treatment and follow up assessments see Table 1.

Table 1. Overview of assessments

Measure	Description	T_0	T_1	T_2	T_3	T_4	T_5	T_6	T_7	T_8	T_{9*}
Interviews											
SCID-I	DSM-IV-TR Axis I disorders	+		+			+				+
HDRS	Depressive symptoms and severity	+		+			+				+
CEQ, only Mobile CT group	Credibility/expectancy questionnaire	+		+							
Implicit computer assignments											
IAT	Implicit associations	+		+							
RSVP	Ability to disengage from negative information	+		+							
Self report measures											
IDS-SR_{30}	Depressive symptoms	+	+	+	+	+	+	+	+	+	+
RSQ	Ruminative responses	+	+	+			+				+
EQ-5D	Quality of life	+		+	+	+	+	+	+	+	+
DAS	Dysfunctional Attitudes	+	+	+			+				+
AAQ	Experiential acceptance and avoidance	+	+	+			+				+
UCL	Coping	+	+	+			+				+
LGV	Life-events	+		+			+				+
Self-esteem	Self-esteem	+	+	+			+				+

PDQ-4+	Personality	+					+				+
Nemesis Somatic illnesses list	List of somatic disorders	+					+				+
EPCL	Everyday problem list	+	+	+	+	+	+	+	+	+	+
HCL-32	Hypomania	+	+	+	+	+	+	+	+	+	+
TIC-P including MAQ**	Direct/indirect costs	+		+	+	+	+	+	+	+	+
LEIDS	Dysfunctional attitudes	+	+	+			+				+
Mastery 7	Mastery	+	+	+	+	+	+	+	+	+	+

Note, *T0=Baseline, T1=±1,5 months,T2=3 months, T3=6 months, T4=9 months, T5=12 months, T6=15 months, T7=18 months, T8=21 months, T9=24 months; **MAQ: Medication Adherence questionnaire.

Primary outcome

Primary outcome is time until relapse or recurrence of depression in the experimental group relative to the control group over 24 months using DSM-IV-R criteria as assessed by the SCID-I at 3 months, 12 months and 24 months. Comorbidity with concurrent chronic somatic illnesses will be assessed using the NEMISIS somatic illnesses list (R. de Graaf et al., 2002). Secondary outcome is symptom severity as measured with the Inventory of Depressive Symptomatology ($IDS\text{-}SR_{30}$) (Rush et al., 1996) and number of relapses as assessed by the SCID (First et al., 2001). For the economic evaluation we will use the EuroQoL (EQ-5D) to obtain a generic quality of life related outcome (EuroQol, 1990). Cost data related to health care uptake will be sampled using the TIC-P (Hakkaart-Van Roijen, 2002). Cost data stemming from production losses due to absenteeism and working less efficiently while at work will be collected with the specific modules from the TIC-P (Hakkaart-Van Roijen, 2002).

Moderators and Mediators

For potential moderators (illness related, stress-related and cognitive-related) predictors and mediators the following self-report measures will be used at baseline, at 1.5 and at 3 months (Internet-based): Inventory of Depression Symptomatology ($IDS\text{-}SR_{30}$ every 3 months) (Rush et al., 1996), Dysfunctional Attitude Scale, (DAS-A) (A. N. Weissman, 1979), LEIDS (van der Does, 2002), Everyday Problem Checklist (EPCL) (Vingerhoets & van Tilburg, 1994), Negative Life Events Questionnaire (Kraaij & de Wilde, 2001) and to assess non-adherence to AD with the Medication Adherence Questionnaire (MAQ) (Morisky et al., 1986), Mastery7 (Pearlin & Schooler, 1978). To

enable calculating quality adjusted life years required for the economic evaluation the EQ5D will be administered every 3 months (EuroQol,1990). To test whether Mobile CT affects implicit attitudes and attentional bias differentially and whether residual difficulty to disengage and residual dysfunctional implicit attitudes are related to the return of depressive symptoms, a web-based Implicit Association Test (IAT) (Greenwald, McGhee, & Schwartz, 1998) will be used to assess implicit attitudes. A web-based rapid serial visual presentation (RSVP) (Koster, De Raedt, Verschuere, Tibboel, & de Jong, 2009) task will be used to assess the difficulty to disengage from negative information. Difficulty to disengage will be indexed by the magnitude of the attentional blink when negative self-descriptors are presented as the first target and neutral words as the second.

Analysis

Cox regression analysis (survival analysis) will be performed, including as covariates the stratification variables that will be used in randomization, i.e. number of previous episodes and type of care (primary/secondary/no care). Analysis will be conducted by intention to treat, including all subjects randomized in the study, and per protocol, including only subjects satisfying protocol. Statistical significance will be set at $p < .05$.

Mixed-model analysis of variance (ANOVA) will be used for the other variables, including baseline values of the dependent variable as a covariate in all analyses. We shall use implicit and explicit cognitive measures and stress measures (daily hassles) to explore the extent to which they mediate relapse and recurrence during treatment and follow up.

For the economic evaluation the balance between costs and health outcomes will be compared across strategies using a societal perspective. Primary outcome measure: the number of depression-free days. Both short-term and long-term consequences will be compared. Additionally, Quality Adjusted Life Years will be used as outcome (see also table 1).

Discussion

Given the high prevalence of MDD and its recurrent character new minimal interventions are needed to prevent relapse and recurrence in depression. Internet-based interventions might be helpful in empowering patients to become their own disease managers in this lifelong recurrent disorder. This is, as far as we are aware of, the first study that examines the (cost) effectiveness of an E-mental health program using SMS and e-mail monitoring of symptoms with therapist support to prevent relapse in remitted recurrently depressed patients. Attrition is a very common phenomenon in Internet-based interventions, hopefully the therapist support in this intervention will reduce attrition rates, as suggested in the meta-analysis of Spek et al (2007). In addition, mediation variables will be examined to get more insight into the most effective ingredients of the Mobile CT used. This might lead to insights that will lead to the development of more targeted interventions.

In summary, given the highly recurrent nature of MDD, new minimal interventions should be developed and evaluated to prevent recurrence in patients at high risk of recurrence, i.e. patients with multiple prior episodes. Internet-based intervention including SMS based monitoring might be promising in disrupting the rhythm of depression, as will be examined in this study. This combination of self-management-monitoring and self-help could be an easily implemented and potential cost effective part of a broader disease-management program of a chronic (recurrent) illness, i.e. MDD.

Appendix 1: Statistical Analysis Plan

All analysis will be conducted in agreement with the intention to treat principle as per the CONSORT statement. Cox regression analysis will be performed, including as covariates the stratification variables that will be used in randomization, i.e.: number of previous episodes, type of care (no/primary/secondary). Statistical significance will be set at p <.05. When adding the intervention to TAU is superior then the relapse/recurrence rate in this condition should be smaller than in the comparator condition (TAU alone). Therefore, we will obtain cumulative relapse/recurrence hazard rate ratios (HRs). To gauge the robustness of the outcomes, the above analyses will be repeated under a completers-only framework.

Since comorbidity with a concurrent chronic somatic illness for which medical attention is received is defined by the American Psychiatric Association as risk factor for future relapse and recurrence (2010), differential response in this group of patients will be examined explicitly. Subgroups that show particularly good response to the intervention will be identified by regressing SCID depression severity on the interaction term of treatment and clinical characteristics of the participants as measured at baseline. Examples of other characteristics are number of previous depressive episodes, age at which the first depression occurred, concurrent personality disorders, concurrent anxiety disorder, experienced life events, some demographic characteristics (like gender) and sense of mastery. In addition, moderator analysis will also be conducted for demographic variables such as gender, age, educational level, partner status, employment status. These variables have been shown to be of prognostic value in depressive disorder. The same set of predictor variables will also be used in an incremental net benefit regression analysis to addresses the research question in what groups the intervention is likely to be particularly cost-effective.

The economic evaluation will be conducted both as a cost-effectiveness analysis with depression-free survival time as the clinical end term, and as a cost-utility analysis with incremental costs per quality adjusted life years (QALYs) gained as the clinical endpoint. For the latter, health-related quality of life, will be assessed with help of the EQ-5D at baseline and follow-ups. Direct medical and direct non-medical cost data are collected with the TIC-P (Hakkaart-Van Roijen, 2002), a widely used health service

receipt interview in economic evaluations. Unit resource use (GP visits, hospital days, etc.) will be multiplied by their appropriate integral cost prices (Oostenbrink, Koopmanschap, & Rutten, 2002). Indirect non-medical cost data related to production losses through work loss days and work cutback days will be sampled with specific modules of TIC-P (Hakkaart-Van Roijen, 2002). For the economic evaluation use will be made of the pertinent guidelines (Langley, 1996; Oostenbrink et al., 2002; Torrance et al., 1996). In other words, analyses will be conducted in agreement with the intention-to-treat principle, the societal perspective will be taken encompassing intervention costs, direct medical costs, direct non-medical costs and indirect costs. The latter will encompass production losses due to absenteeism and due to working less efficient while at work. Production losses will be economically valuated using the friction cost method (Brouwer, Koopmanschap, & Rutten, 1999) as per the Dutch guideline (Oostenbrink et al., 2002). The time horizon will be set at two years and therefore costs and effects will be discounted. Costs and effects will be analyzed simultaneously, incremental cost-effectiveness ratios (ICERs) will be calculated and placed within 95% confidence intervals, 2,500 bootstrap replications of the ICERs will be projected on a cost-effectiveness plane, ICER acceptability curves will be plotted against different willingness-to-pay ceilings and sensitivity analysis will be conducted as a matter of course focusing on uncertainty in the analysis.

Chapter 8

The short-term effect of Mobile Cognitive Therapy

Abstract

Background: The burden of depression is high, mostly due to its recurrent nature. Therefore, continuous monitoring and treatment is advised to high risk of relapse patients by international practice guidelines. An Internet-based cognitive therapy with monitoring by text messages (Mobile CT), added to Treatment as Usual (TAU), might offer a cost-effective way of treating recurrent depression. Method: Remitted patients with at least two previous episodes of depression were randomized to Mobile CT added to TAU (n=126) or TAU only (n=113). A Linear mixed model was used to examine the effect of treatment condition on the three months' course of depressive symptoms after remission. Depressive symptoms were assessed with the Inventory of Depressive Symptomatology (IDS-SR$_{30}$) at baseline, 1.5, and three months' after randomization. Results: Residual depressive symptoms showed a small but statistically significant decrease in the intention to treat group, over three months in the Mobile CT group relative to the TAU group (difference: -1.63 points on the IDS-SR$_{30}$ per month, 95% CI=-2.57, -0.69). The effect of treatment condition on depressive symptomatology at the three-month follow-up was small to moderate (Cohen's d=0.44). All analyses among completers (>5 modules) showed more pronounced treatment effects. Adjustment for unequally distributed variables did not markedly affect the results. Conclusions: Residual depressive symptoms after remission showed a more favorable course in the Mobile CT group compared with the TAU group. These results are a first indication that Mobile Internet-based CT added to TAU is effective in treating recurrently depressed patients in remission.

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Introduction

According to the Global Burden of Disease study (GBD, 2010), the highest proportion of the total burden of disease of all mental and substance use disorders is caused by Major Depressive Disorder (MDD) (Whiteford et al., 2013). MDD is a highly recurrent disease (Burcusa & Iacono, 2007). Effective treatment strategies for the prevention of relapse are crucial to reduce the burden of depression (Beshai et al., 2011). The longer patients remain well, the lower the risk of relapse (Keller, Shapiro, Lavori, & Wolfe, 1982). Cognitive Therapy (CT) after the acute phase of depression reduces the risk of relapse (Jarrett et al., 2001; D. N. Klein et al., 2004; Paykel et al., 1999; Perlis et al., 2002; Scott et al., 2000; Stangier et al., 2013; Vittengl et al., 2007). In addition, brief psychotherapy, i.e. Preventive CT, Well-Being Therapy and Mindfulness based CT, lowers relapse rates compared to treatment as usual (TAU) as well (Bockting et al., 2005; Bockting et al., 2009; G. A. Fava et al., 1994; G. A. Fava et al., 1996; G. A. Fava et al., 1998; G. A. Fava, Rafanelli et al., 1998; Guidi et al., 2011; Ma & Teasdale, 2004; Piet & Hougaard, 2011; Teasdale et al., 2000). Importantly, Mindfulness based CT and Preventive CT are more effective in patients with a higher number of previous episodes (Bockting et al., 2005; Bockting et al., 2009; Jarrett et al., 2001; Ma & Teasdale, 2004; Piet & Hougaard, 2011; Stangier et al., 2013).

Clinical practice guidelines for MDD treatment recommend long-term monitoring and guidance for patients with recurrent episodes and/or residual depressive symptoms (American Psychiatric Association, 2010; Andrews, 2001; National Institute for Health & Care Excellence, 2010). However, resources are generally scarce and there is limited availability of therapists (Cameron & Thompson, 2005; Saxena, Thornicroft, Knapp, & Whiteford, 2007). Therefore, Internet-based CT including monitoring by text messages and therapist support by telephone (Mobile CT) may be a feasible approach. Internet-based CT is easily accessible and therapist involvement may be reduced, as demonstrated in acute phase Internet-based treatment (Wright et al., 2005). In addition, monitoring by text messages allows relapse detection by patient and therapist as early as possible. So far, only one study has examined the effect of an internet-based cognitive behavior therapy (CBT) compared to a control group on reduction of

depressive symptomatology and subsequent course of symptomatology in patients that responded to treatment but were partially remitted (Holländare et al., 2011; Holländare et al., 2013). They found a trend towards a further reduction of depressive symptoms over six months of the ongoing depressive episode and lowered relapse rates over two years in the Internet CBT group (Cohen's d pre-to post treatment effect = 0.33, with the MADRS-S and d = 0.29 with the BDI-II). However, no study has been conducted using these technologies aimed at relapse prevention of a new episode in patients remitted for at least two months. In the current randomized controlled trial the effect of Mobile CT added to TAU on the three months' course of depressive symptomatology, was compared to TAU in remitted recurrently depressed patients.

Method

To be included in the randomized controlled trial (Bockting, Kok et al., 2011), participants a) had to be between 18 and 65 years of age, b) had to be in remission of recurrent MDD for at least two months, but no longer than two years according to DSM-IV-TR as assessed using the Structured Clinical Interview based on the Diagnostic and Statistical Manual of Mental Disorders (SCID-I, DSM-IV-TR) (First et al., 2001) and a maximum score of 10 on the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$) (Hamilton, 1960). Further participants had to have Internet access. Exclusion criteria assessed by the SCID-I interview were: 1) a predominant anxiety disorder that needed treatment 2) current or past mania or hypomania 3) current alcohol-or drug abuse 4) past or present psychosis. Additional exclusion criteria were insufficient mastery of the Dutch language, recent electroconvulsive therapy and organic brain damage. The study was approved by the Medical Ethics Committee of the University Medical Center Groningen and all participants provided written informed consent.

Study design

Participants were recruited via media, general practitioners and mental health care institutions. When interested, participants provided the researchers with their contact information, after which the researchers contacted and screened them with a short form

over the telephone. When deemed eligible, a SCID-I interview and $HRSD_{17}$, were scheduled and performed over the telephone by trained researchers and psychologists. All interviews were audiotaped and regular consensus meetings were held under the supervision of a clinical psychologist. Interviewers were blind for treatment condition. After inclusion, participants received an e-mail with a link to a series of online self-report questionnaires. Randomization to treatment condition took place after completion of the online self-report questionnaires (T_0), at an individual level. Randomization was undertaken by an independent researcher and stratified by type of care (i.e. no care versus mental health care or antidepressant medication) and number of previous depressive episodes (2 versus ≥ 3 episodes).

Treatment

Mobile CT was based on a previously evaluated face-to-face Preventive CT (Bockting et al., 2005; Bockting et al., 2009; Bockting, 2009; Bockting, Kok et al., 2011). In brief, PCT consists of eight structured sessions including cognitive interventions specifically developed to prevent relapse in recurrent depression in remitted patients. Participants were advised to do one module per week. Mobile CT was completely offered over the Internet with minimal therapist support, i.e. a maximum of 4 telephone sessions. Each module included assignments with automatically generated feedback and could be completed in approximately 20 minutes. Automated checks were conducted to ascertain that participants had completed the modules and understood them correctly. After completion of all assignments, a personal prevention of relapse book was automatically generated. Participants received friendly reminders by text message or e-mail to proceed with the intervention after absence of six weeks. The researchers scheduled at least two voluntary telephone sessions with trained mental health psychologists. Therapist support was aimed at working through the modules and finishing the therapy (based on: Andersson, Lundström, & Ström, 2003; C. Williams & Morrison, 2010). Participants could ask for at most two additional telephone sessions and send e-mails without frequency restrictions.

Mobile mood monitoring: twice a month, participants in the Mobile CT group received a text message or e-mail to fill in a mood monitor, consisting of two questions

about last week's mood and interests in order to check for the two core symptoms of depression (American Psychiatric Association, 2000), to be answered on a Likert-type scale ranging from 1 to 10. In case a decrease in mood or interests occurred twice in a row (score of < 3), participants automatically received a request to fill in the 16 item Quick Inventory of Depressive Symptomatology (QIDS) (Rush et al., 1996). When the score exceeded 10, indicated suicidal ideation, the researchers checked for relapse by administering the $HRSD_{17}$ and the depression section of the SCID-I. In case the $HRSD_{17}$ score was ten or higher and the SCID-I was indicative of a DSM-IV-TR relapse, participants were advised to contact their general practitioner or therapist.

TAU could consist of multiple types of treatment, such as antidepressant medication treatment, maintenance or continuation therapy by a psychologist or psychiatrist or no treatment at all. There were no restrictions to type of TAU. In the TAU condition, participants did not receive text message based monitoring, although like in the experimental condition regular assessments were done using the Inventory of Depressive Symptomatology ($IDS\text{-}SR_{30}$) (Rush et al., 1996) (8 times after baseline) and SCID-I (3 times after baseline). In case of a depressive relapse, participants were advised to contact their general practitioner or therapist (if available).

Outcome measures

The primary outcome measure was the three-month course of self-reported residual depressive symptoms in 1) Mobile CT added to TAU and 2) TAU alone. Depressive symptomatology was assessed at baseline, 1.5 months after randomization (T1) and three months after randomization (T2), using the Dutch translation of the $IDS\text{-}SR_{30}$ (Rush et al., 1996). The inventory consists of 30 symptom items to be answered on a 4-point Likert-scale, ranging from 0 (no symptom) to 3 (almost always troubled by symptom). A score of 0-13 is categorized as no symptoms, 14-25 are mild symptoms, 26-38 moderate symptoms, 39-48 severe symptoms and above 49 very severe symptoms. Its reliability as assessed in the present study was good with a Cronbach alpha of .87, which is in accordance with values reported by Rush et al (1986) α=.79-.85).

The 17-item HRSD was used to assess baseline depressive symptom levels. The $HRSD_{17}$ was administered over the telephone by trained researchers and psychologists before treatment allocation. The HRSD is an often used semi structured clinical interviews. Scores can range from 0 to 52 (Hamilton, 1960). The internal consistency appears to be adequate in this study with a Cronbachs alpha of .66.

Data analyses

The primary analysis was performed in agreement with the intention to treat (ITT) principle, including all randomized patients, regardless of treatment adherence, drop-out and completeness of outcome assessments. To check whether randomization had been successful, we first described the study population according to treatment group by calculating means and standard deviations for continuous variables and percentages for categorical variables. A Linear Mixed Model (LMM) was used to examine differences in the linear rate of change between the randomized groups in depressive symptoms over the three-month course, i.e. the treatment effect. LMM is the preferred method for analyzing multivariate longitudinal data (Peduzzi, Henderson, Hartigan, & Lavori, 2002). LMM makes optimal use of the available data because incomplete cases are included in the analyses under the assumption that missing data are missing at random. A LMM was fitted with the IDS-SR_{30} score as the dependent variable and as independent variables time (unit: month). The apparent non-linearity in the rate of change of the IDS-SR_{30} score was accommodated by including a time-squared variable. Whilst thus taking into account an overall quadratic time trend, we included a between group-by- time interaction, to represent the between group difference in the linear rate of change. Dependency of the repeated assessments of depression within the same participant was taken into account by adding a random intercept and random slope for participants using an unstructured variance-covariance matrix. Removal of the random slope worsened the fit of the model in a statistically significant way and it was therefore retained. Similarly, a secondary LMM analysis was conducted based on the completers group. Completion was defined as finishing at least five out of the eight modules of Mobile CT. Both the ITT and the completers analysis was supplemented with analyses in which we adjusted for the stratification variables, the duration of remission and for

possible imbalances in baseline prognostic factors between the randomized groups. We conservatively defined the effect size of three-month treatment as the crude difference between the randomized groups in the mean IDS-SR_{30} scores at the final assessment and expressed it as Cohen's d. We included 239 patients allowing us to demonstrate statistically significant effect sizes of 0.36 or over with 80% power (1-beta) at a two-sided significance level of 5% SPSS version 20.0 was used where we considered a two-sided p <.05 to be statistically significant.

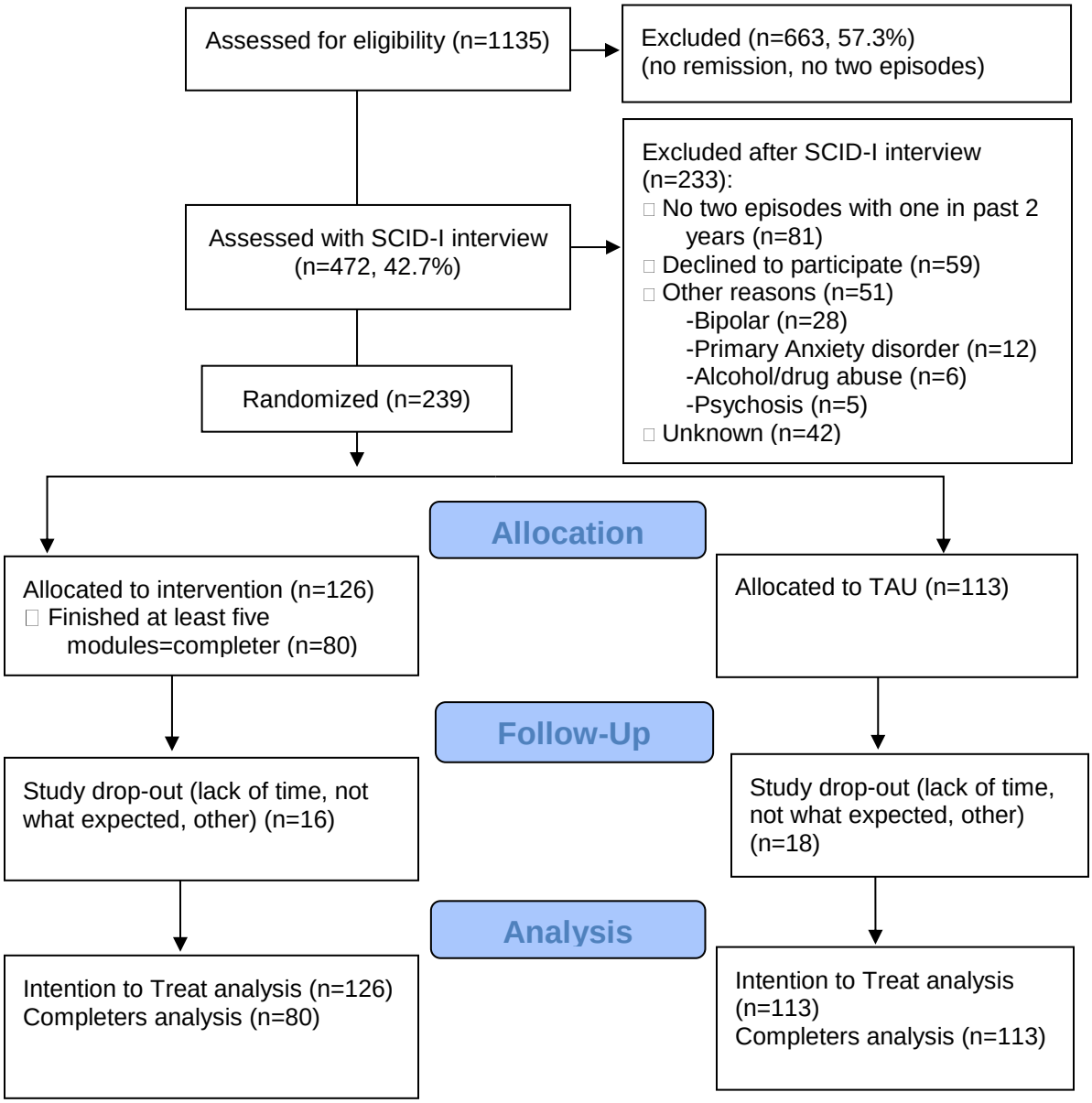
Results

Baseline characteristics and study flow

Out of 1157 patients screened for eligibility, 663 patients (57.3%) did not meet the inclusion criteria after the first screening. This led to 494 patients (42.7%) that were interviewed with the SCID-I. Most patients (n=81) were excluded because they did not have two previous episodes and finally 239 patients (20.7%) were randomized (stratified on treatment as usual and the number of previous episodes). Figure 1 provides an overview of the number of participants and drop-outs at each follow-up.

The highest proportion of the included patients was recruited via media (64.4%). After completion of the baseline questionnaires, patients were randomized to either TAU (n=113) or Mobile CT added to TAU (n=126). In Table 1 baseline demographics of the ITT group are presented. The median number of previous depressive episodes was four in both the Mobile CT and TAU group (IQR, respectively=2.3-2.5). In both groups the mean time since the last episode was around eight months (TAU: M=7.98, SD=6.2; MCT: M= 8.23, SD=6.5). For 38.1% of the Mobile CT and 37.2% of the TAU group, TAU consisted of no treatment at all, 47.6% of the Mobile CT and 51.3% of the TAU group received antidepressant medication treatment and 21.4% of the Mobile CT and 21.2% of the TAU group received care by a mental health professional (e.g. psychologists, psychiatrist).

Figure 1. Consort Flow Diagram of participant flow over three-month follow-up



Most variables were equally distributed between the groups at baseline (p >.05). However, the TAU group had an overall higher severity of the last episode, assessed with the SCID-I, compared to the Mobile CT group (30.1% TAU versus 15.9% Mobile CT, p =.029). Therefore, additional ITT analyses were performed while controlling for this variable.

Table 1. Baseline demographic and descriptive characteristics of the study population according to randomized group[4]

	Mobile CT (N=126)	TAU (N=113)
Age, mean (SD)	45.52 (10.9)	47.48 (10.8)
Female gender, no. (%)	100 (79.4)	79 (69.9)
Marital status, no. (%)		
Single	38 (30.2)	29 (25.7)
Married or cohabiting	76 (60.3)	71 (62.8)
Divorced	8 (6.3)	11 (9.7)
Widowed	2 (1.6)	0 (0.0)
Missing	2 (1.6)	2 (1.8)
Education, no. (%)		
Primary school	1 (0.8)	1 (0.9)
Secondary education	5 (4.0)	8 (7.1)
Vocational education	40 (31.7)	31 (27.4)
Pre-university education	2 (1.6)	3 (2.7)
Higher education	53 (42.1)	44 (38.9)
University	25 (19.8)	21 (18.6)
Missing	0 (0.0)	5 (4.4)
ADM at recruitment, no. (%)	60 (47.6)	58 (51.3)
Treatment by mental health professional, no. (%)	27 (21.4)	24 (21.2)
Age of first MDD episode, mean (SD)	28.67 (12.3)	30.11 (13.1)
Previous episodes MDD, median (IQR)	4.0 (2.3)	4.0 (2.5)
Total $HRSD_{17}$, mean (SD)	3.58 (2.8)	3.42 (2.9)
Depressive symptomatology ($IDS\text{-}SR_{30}$), mean (SD)	16.44 (10.5)	16.06 (9.5)
Severity last episode, no. (%)[a]		
Minor	33 (26.2)	23 (20.4)
Moderate	71 (56.3)	56 (49.5)
Severe	20 (15.9)	34 (30.1)
Missing	2 (1.6)	0 (0.0)

Note, ADM=Antidepressant medication; MDD=Major Depressive Disorder; [a] Last episode severity is based on the number of SCID-I depression symptoms (5 symptoms corresponds to minor, 6-7 symptoms corresponds to moderate, whereas 8-9 symptoms corresponds to severe depression); $HRSD_{17}$=depressive symptoms; $IDS\text{-}SR_{30}$=depressive symptomatology.

[4] All baseline variables were equally distributed p>.05, except for the severity of the last episode p=.029

During follow-up, a total of 34 (14.2%) participants dropped-out of the trial (n=13 in both groups at 1.5 months, n=3 in the Mobile CT group and n=5 in the TAU group at 3 months). Of the 126 participants randomized to the Mobile CT added to TAU group, 113 participants finished the first module and 80 participants (63.5%) finished at least five modules, the last being defined as being a completer. All variables at baseline were equally distributed in the Mobile CT and TAU condition in the completers group. In addition, there were no substantial differences between the ITT and completers group (all *p*'s >.05). However, the ITT group had an earlier age at first onset of depression than the completers (*p* =.029, respectively: M=26.23, SD=10.6; M=30.07, SD=13.0).

Mobile CT usage

Full adherence (all eight modules finished) was 53.1% (60/113 participants). Of all completers 80% (n=64/80) finished at least five modules within three months. The mean amount of total time per therapist per participant during the complete Mobile CT was 18 minutes (SD=8.2). While each participant was invited for a second telephone session with the therapists, only 56.5% of the 113 participants used this option. The percentage of participants that asked questions by e-mail was 40.5%. Mobile mood monitor: Of the 113 participants that finished the first module, over follow-up 13 participants rated their mood and interests as lower than three, twice in a row. Their therapists received an automated message of this. Of these, six filled in the Q-IDSR-$_{16,}$ after getting an automatic request.

Three-month course of depressive symptoms in Mobile CT and TAU group

Depressive symptoms measured with the IDS-SR$_{30}$ increased from baseline to 1.5 months of follow-up in both groups (table 2). However, after three months of follow-up a small decrease was observed in the Mobile CT group and a considerable increase was noticeable in the TAU group. The results of the LMM analyses are presented in Tables 3 and 4. There was a significant linear time trend (F=13.134, *p*<.001) and a significant time squared trend (F=6.881, *p*=.009). The interaction between time and treatment indicating the difference in the linear rate of change between groups, i.e. treatment effect, was statistically significant (F=11.608, *p* =.001). Compared to the TAU group, the

rate of change in IDS-SR_{30} score in the Mobile CT group was -1.63 points per month (t=-3.407, *p* =.001, 95% CI=-2.57, -0.69) (table 3a). Repeating the analysis in the completers group (≥ 5 modules of Mobile CT) showed a larger treatment effect with a between group difference of -2.04 points per month (t=4.197, *p* < .0001, 95% CI=-2.99, -1.08) (table 3b). Adjusting for severity of the last episode, duration of remission and the stratification variables type of TAU and the number of previous episodes did not affect the results of the ITT analysis (table 4a) nor the results of the completers group (table 4b). Cohen's d for the treatment effect on depressive symptoms over three months was 0.44, which indicates a small to moderate effect. In addition, depressive symptom levels measured with the $HRSD_{17}$ interview demonstrated higher depressive symptom levels at three-month follow-up in the TAU group compared to the Mobile CT group as well (M=5.44, SD=6.1 in TAU versus M=4.25, SD=4.3 in Mobile CT, *p* =.042).

Table 2. Three-month course of depressive symptoms in the Mobile CT and TAU group, in the ITT group

Depressive symptomatology	Mobile CT		TAU	
	M	SD	M	SD
Baseline	16.44	10.5	16.06	9.5
6 weeks	18.61	12.2	20.76	12.1
3 months	16.38	10.9	21.52	12.4

Table 3a. Three-month course of depressive symptoms in the Mobile CT and TAU group, unadjusted estimates in the ITT group

Variable	Estimate	95%,CI	T	*p*
Intercept	16.288	[14.87, 17.70]	22.644	.000
Time	4.212	[2.30, 6.12]	4.341	.000
$Time^2$	-0.816	[-1.43, -0.20]	-2.623	.009
Mobile CT*Time	-1.629	[-2.57, -0.69]	-3.407	.001

Table 3b. Three-month course of depressive symptoms in the Mobile CT and TAU group, unadjusted estimates in the completers group

Variable	Estimate	95%,CI	T	*p*
Intercept	16.313	[14.77, 17.86]	20.743	.000
Time	1.989	[0.05, 3.93]	2.017	.045
Time^2	-0.749	[-1.36, -0.14]	-2.406	.017
Mobile CT*Time	2.036	[1.08, 2.99]	4.197	.000

Table 4a. Three-month course of depressive symptoms in the Mobile CT and TAU group, adjusted estimates in the ITT group

Variable	Estimate	95%,CI	T	*p*
Intercept	13.444	[9.35, 17.54]	6.463	.000
Time	4.131	[2.22, 6.04]	4.259	.000
Time^2	-0.806	[-1.42, -0.19]	-2.593	.010
Mobile CT*Time	-1.551	[-2.49, -0.61]	-3.236	.001
Severity of last episode	1.598	[-0.24, 3.44]	1.708	.089
Duration of remission	-0.088	[-0.29, 0.11]	-0.882	.379

Table 4b. Three-month course of depressive symptoms in the Mobile CT and TAU group, adjusted estimates in the completers group

Variable	Estimate	95%,CI	T	*p*
Intercept	15.149	[10.90, 19.39]	7.038	.000
Time	1.965	[0.02, 3.90]	1.993	.047
Time^2	-0.743	[-1.35, -0.13]	-2.386	.018
Mobile CT*Time	2.040	[1.09, 2.99]	4.211	.000
Duration of remission	-0.103	[-0.32, 0.12]	-0.924	.357

Discussion

To the best of our knowledge, this is the first study examining the effect of Mobile Internet-based CT with minimal therapist support as relapse prevention strategy in completely remitted recurrently depressed patients. Given that depressive symptom levels were very low at baseline ($HRSD_{17}$ M=3.52, SD=2.9), symptoms were likely to increase over time (Keller et al., 1982). Notwithstanding this expectation, a small but significant decrease in depressive symptoms over follow-up was observed in the Mobile CT condition, but not in the TAU condition in which a pronounced increase was found.

The difference between the groups was -1.63 points on the IDS-SR_{30} per month, which was small but statistically significant. The difference between groups was considerably larger when participants finished at least five modules of Mobile CT This corroborates with previous research demonstrating effectiveness of Internet-based psychotherapies to increase when treatment adherence is higher (Hilvert-Bruce, Rossouw, Wong, Sunderland, & Andrews, 2012). Our findings are also in line with a study in a slightly different population, i.e. in partially remitted depressed patients (Holländare et al., 2011; Holländare et al., 2013). In this study (n=84), a trend towards a six-month decrease in depressive symptoms after Internet preventive CBT was reported (Holländare et al., 2011). In addition, previous studies found face-to-face CT and MBCT offered after the acute phase to be equally effective in reducing residual depressive symptoms (Andersson et al., 2013; G. A. Fava et al., 1994; Kuyken et al., 2008).

The mean 18 minutes of total therapist support time per participant (telephone and e-mail), was far less than mostly found in other studies where the total time ranges from 180 minutes to 352 minutes (Carlbring et al., 2006; B. Klein et al., 2009). However, the 53.1% adherence to Mobile CT was comparable to adherence to Internet-based psychotherapies in other randomized controlled (50-85%) (e.g. Christensen, Griffiths, & Farrer, 2009). This might indicate that even with less therapist support an Internet intervention might be effective. However, this could only hold for remitted patients and not for the depressed phase. More information on the topic of support and adherence is needed.

Presence and fluctuations of residual depressive symptoms are well known predictors of relapse (American Psychiatric Association, 2010; G. A. Fava et al., 1994; Judd et al., 1998; Karp et al., 2004; ten Doesschate et al., 2010). Residual symptoms may progress to become prodromal symptoms of relapse, and targeting residual symptoms might yield long-term benefits (G. A. Fava & Kellner, 1991; Guidi et al., 2011). Previous research demonstrated that the longer patients remained well, the lower the risk of relapse (Keller et al., 1982). Mobile CT might prolong remission time in recurrently depressed remitted patients. Judd, Paulus and Zeller (1999), suggest that prevention of relapse is related to the reduction of residual symptoms. However, an effect of treatment on relapse is not proven to be dependent on lowering residual

symptom levels (Bockting et al., 2006; Paykel et al., 1999; Scott et al., 2000). A longer follow-up will be needed to examine whether the effect of Mobile CT on relapse is mediated by a decrease in residual symptoms. Alternatively, other potentially modifiable vulnerability factors might mediate the effect on relapse, such as dealing with (daily) stress. Daily stress was found to predict depressive relapse (Bockting et al., 2006; G. A. Fava et al., 1996; Monroe et al., 1996; Ormel et al., 2001), however after preventive cognitive therapy daily stress did not predict relapse anymore (Bockting et al., 2006).

Limitations

Although these first results on the low intensity preventive treatment Mobile CT added to TAU are promising, they have to be interpreted in light of some study limitations. First, replication of these findings with a longer follow-up is required before firm conclusions can be drawn on the long term preventive effects of Mobile CT as add on to TAU. The difference in depressive symptoms in both groups might seem small; however during the remission even small increases in depressive symptoms are predictive of relapse (Judd et al., 1998). In addition, at the three-month follow-up the effect of treatment was small to moderate. Second, the information on depressive symptoms was restricted to the follow-up assessments, therefore variations in-between could have been missed. Third, although a high proportion (80%) of the completers finished the modules before three months, for a few patients it took longer to finish the modules. This implies that after three-month follow up, not all participants finished all modules (n=16). However, the analysis in the ITT sample showed similar results. Fourth, although the SCID-I interview is known as the gold standard in assessing current and lifetime depression, we performed the SCID-I interview by telephone. This could influence the validity; however in previous studies diagnostic interviews by telephone have proven to be valid (Rohde, Lewinsohn, & Seeley, 1997). Further, the number of previous episodes of depression was retrospectively assessed with the SCID-I and recall could have been affected by memory bias. Finally, we did not control for effects of all non-specific factors.

Conclusion and implications

For recurrently depressed patients ongoing monitoring and preventive treatment is internationally recommended by clinical guidelines (American Psychiatric Association, 2010; National Institute for Health & Care Excellence, 2010). Mobile CT combines an Internet-based intervention with minimal mobile therapist support (mean 18 minutes per patient in total) and monitoring of mood by text messages. This is the first study that demonstrates promising effects of Mobile CT on residual depressive symptoms in remitted recurrently depressed patients as compared to TAU, irrespective of type of TAU including antidepressant medication treatment. Our results indicate the potential of Mobile CT added to TAU in treating residual depressive symptoms in recurrently depressed patients remitted up to two years. Replication is necessary and future studies should examine the preventive effects of Mobile CT compared to face to face preventive strategies.

Chapter 9

Adherence and acceptability of Mobile Cognitive Therapy

Abstract

Background: There are first indications that an Internet-based cognitive therapy (CT) combined with monitoring by text messages (Mobile CT), and minimal therapist support (e-mail and telephone), is an effective approach of prevention of relapse in depression. However, examining the acceptability and adherence to Mobile CT is necessary to understand and increase the efficiency and effectiveness of this approach. Method: In this study we used a subset of a randomized controlled trial on the effectiveness of Mobile CT. A total of 129 remitted patients with at least two previous episodes of depression were available for analyses. All available information on demographic characteristics, the number of finished modules, therapist support uptake (telephone and e-mail), and acceptability perceived by the participants was gathered from automatically derived log data, therapists and participants. Results: Of all 129 participants, 109 (84.5%) participants finished at least one of all eight modules of Mobile CT. Adherence, i.e. the proportion who completed the final module out of those who entered the first module, was 58.7% (64/109). None of the demographic variables studied were related to higher adherence. The total therapist support time per participant that finished at least one module of Mobile CT, was 21 minutes (SD=17.5). Overall participants rated Mobile CT as an acceptable treatment in terms of difficulty, time spent per module and usefulness. However, one therapist mentioned that some participants experienced difficulties with using multiple CT based challenging techniques. Conclusion: Overall uptake of the intervention and adherence was high with a low time investment of therapists. This might be partially explained by the fact that the intervention was offered with therapist support by telephone (blended) reducing non-adherence and that this high-risk group for depressive relapse started the intervention during remission. Nevertheless, our results indicate Mobile CT as an acceptable and feasible approach to both participants and therapists.

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Introduction

Major Depressive Disorder (MDD) is a chronically relapsing disease (D. Richards, 2011), with a high risk of depressive relapse (Burcusa & Iacono, 2007). Each episode of depression leads to considerable economic costs to the society (Johnson, Weissman, & Klerman, 1992; Keller & Boland, 1998; D. Richards, 2011; Smit, 2009). Prevention of relapse is therefore of great importance. However, waiting lists due to scarcity of therapists are common (Cameron & Thompson, 2005). Therefore, an Internet-based Cognitive Therapy might be a feasible approach, given that it is easily accessible and therapist involvement may be reduced, as demonstrated in acute phase Internet-based treatment (Wright et al., 2005). Meta-analyses demonstrated small to moderate effect sizes of Internet-based therapies in the acute phase of depression, anxiety, panic disorders and alcohol use disorders (Andersson, Cuijpers, Carlbring, Riper, & Hedman; G. Andersson & Cuijpers, 2009; Lewis, Pearce, & Bisson, 2012; D. Richards & Richardson, 2012; Riper et al., 2011; Spek et al., 2007). In addition, first results of psychological treatment by using a smartphone app are positive as well (Ly, Dahl, Carlbring, & Andersson, 2012; Ly et al., 2014).

There are first indications that the effects of guided self-help interventions (blended care), such as Internet-based psychotherapy, might be comparable to face-to-face psychotherapy, although this is less clear to patients seeking help in specialty care (Andersson et al., 2013; Cuijpers, Donker, van Straten, Li, & Andersson, 2010).

Although it was demonstrated that Internet-based therapies are effective in treating various (mental) health problems, most studies were performed in patients with acute problems. So far, only one study has examined an Internet-based Cognitive Behavior Therapy (CBT) compared to a control group as a relapse prevention strategy in depressed patients that responded to treatment but were partially remitted (Holländare et al., 2011; Holländare et al., 2013). Now for the first time, an Internet-based preventive Cognitive Therapy aimed at relapse prevention of a new episode in patients remitted for at least two months, including mood monitoring by making use of text messages and minimal therapist support by telephone and e-mail (Mobile CT) was developed and evaluated (Bockting & van Valen, 2009; Bockting, 2009). Recently, in a randomized

controlled trial (N=239), we demonstrated that Mobile CT significantly reduced depressive symptoms levels measured with the Inventory of Depressive Symptomatology ($IDS\text{-}SR_{30}$), over three months of follow-up compared to Treatment as Usual in fully remitted participants with recurrent depression (Cohen's d=0.44; Kok et al., 2014 *under review*).

Apart from these effects on return of depressive symptomatology, understanding how and to what extent an intervention is used is critical to increase the efficiency and efficacy (Eysenbach, 2005). According to the model of Internet-based interventions by Ritterband et al (2009), based on multiple theories and models, factors such as user characteristics, adherence, support and website characteristic all influence the usage of the Internet-based intervention. In the current study, after we described the details of the Mobile CT program that was developed, the following facets were examined to evaluate the use of Mobile CT: 1) the user characteristics of participants in relation to adherence, 2) therapist support uptake, 3) experienced difficulties based on some experiences of participants and therapists and evaluations filled in by participants after each module of Mobile CT.

Method

In this study we used a subset of a randomized controlled trial on the effectiveness of Mobile CT aimed at the prevention of depressive relapse (the first 129 participants that entered the study and were currently available for analyses) (Bockting et al., 2011). Participants were recruited via media, general practitioners and mental health services. The present quantitative and qualitative analyses were performed in the participants that were randomized into the Mobile CT added to TAU condition. Participants were a) between 18 and 65 years of age, b) in remission of recurrent MDD for at least two months, but no longer than two years according to DSM-IV-TR as assessed using the Structured Clinical Interview based on the Diagnostic and Statistical Manual of Mental Disorders (SCID-I, DSM-IV-TR) (First, Spitzer, & Gibbon, 2001) and had a maximum score of 10 on the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$) (Hamilton, 1960). Excluded participants had 1) a predominant anxiety disorder 2) current or past

mania or hypomania 3) current alcohol-or drug abuse 4) past or present psychosis based on the SCID-I interview. Additionally those persons with insufficient mastery of the Dutch language, recent electroconvulsive therapy or organic brain damage were not included. The study was approved by the Medical Ethics Committee of the University Medical Center Groningen and all participants provided written informed consent.

The Mobile Cognitive Therapy

Mobile CT consists of Internet-based Preventive Cognitive Therapy (PCT), telephone delivered psychotherapy (telemental health) and mood monitoring via text messages and e-mail. Mobile CT consists of eight modules with a fixed structure and is an adapted form of PCT. PCT is an effective eight session face to face intervention aimed at the prevention of relapse in remitted but recurrently depressed patients (Bockting et al., 2005; Bockting et al., 2009). When participants log into the web-based intervention, they first see the “cockpit”, which consists of 1) an overview of the eight modules, 2) mood monitor information, 3) e-mail communication with their therapist (coach). Via the cockpit other parts of the intervention can be assessed as well, such as additional prevention of relapse information and a personal workbook in which participants can save exercises from the modules. The workbook further contains records of negative and positive thoughts and feelings. The workbook can be personalized by adding a photo of oneself and writing a motivational message to oneself. After study participants logged in for the first time, they were obliged to fill in whether they wanted to receive the mood monitor and reminders via text messages by mobile telephone or e-mail. Access to subsequent modules is only granted after finishing the previous module.

Each module consists of text and video based information and assignments that can all be finished in approximately 20 minutes. In the present study, participants were advised to finish around one module each week, but were told to repeat modules as often as they wanted. Every study participant had access to Mobile CT for one year and could log in as often as they wanted, also after finishing all modules. Mobile CT has been developed in a collaboration between the University of Groningen and the Trimbos-institute (Netherlands Institute of Mental Health and Addiction).

Mobile mood monitoring

Twice a month, participants received a reminder via a text message (or e-mail on request by the participant) to fill in the mood monitor. The mood monitor consists of two questions about last week's mood and interests, in order to check the two key symptoms of depression (American Psychiatric Association, 2010), to be answered on a scale of 1 to 10. In case a decrease in mood or interests occurred twice in a row (score of < 3), participants received an automatic request to fill in the 16 item Quick Inventory of Depressive Symptomatology (QIDS) (Rush et al., 1996). In case the outcome of the QIDS was a score above 10, or indicated suicidal ideation, the researchers checked return of a depressive episode with an interview (i.e. the $HRSD_{17}$ and the depression section of the SCID-I). In case the $HRSD_{17}$ score was ten or higher and the SCID-I was indicative of a depressive relapse, participants were advised to contact their general practitioner or therapist.

Automatic feedback and reminders

Each participant received friendly reminders by text message or e-mail to proceed with the intervention after absence to the website for six weeks. Further, in the beginning of each module after the first, participants were asked if they finished the assignment in the previous module. Depending on their answer, participant received automatic feedback. For example, when a participant filled in that the previous exercise was performed, the system answered: **Very good!** By practicing with assignments you do not only learn the theory but also learn how to apply this in daily life. This makes the training more effective. When a participant filled in that the previous exercise was not performed, the system answered: **Too bad!** By doing assignments you not only learn the theory, but also learn how to use this in daily life. This will make the training more effective. What was the reason for not doing the exercise?

Therapist support

The main aim of overall support was to help participants with the exercises and work through the modules. Participants were assigned to a therapist and approached through e-mail by the researchers to schedule two telephone support sessions with this therapist. In case of no response, participants received friendly reminders by e-mail and telephone, with a maximum of four attempts. Four licensed clinical psychologists, received a one-day training in Mobile CT, including a training in blending the Mobile CT with telephonic, and e-mail support. All therapists received a short protocol for each telephone session (for the protocol see box 1 and 2). The telephone support sessions were scheduled around modules two and five. These telephone sessions were only scheduled when participants reached these modules. We chose modules two and five because in our pilot we had some indications that these modules were the most complicated and to prevent drop out. Additional telephone support sessions were on demand of the participant, with a maximum of two. E-mail contact with the therapist was not scheduled and could be initiated by all participants without restrictions to the quantity.

To promote protocol integrity of therapists, regular Skype meetings were held with all therapists, in which for instance a question like how to deal with difficulties with applying challenging techniques, was discussed.

Before starting with Mobile CT, all participants received standardized information through telephone and e-mail in which they were informed about the modules after which they would be approached telephone sessions with their therapist and the option to ask for additional sessions (with a maximum of four appointments in total) and initiate e-mail contact with their therapist without restrictions to the quantity.

Data collection

User characteristics

As part of the randomized controlled trial, age, education, gender, marital status, number of previous episodes and remission status of all participants allocated to Mobile CT were assessed with the baseline interview using the SCID-I and the $HRSD_{17}$. The

SCID-I was administered by trained researchers over the telephone. The two most recent episodes of depression were assessed at symptom level in the SCID-I interview. All other episodes were assessed by the core DSM-IV-TR criteria depressed mood (A1) or loss of interest (A2). The $HRSD_{17}$ is a semi structured clinical interview to assess depressive symptoms. Scores can range from 0 to 52 (Hamilton, 1960). After the interview, participants received self-report questionnaires through e-mail. The Dutch translation of the Inventory of Depressive Symptomatology was used to measure depressive symptoms at baseline (Rush et al., 1996). The inventory consists of 30 items to be answered on a 4-point scale, ranging from 0 (no symptom) to 3 (almost always troubled by symptom).

Box 1. Therapist protocol for telephone support session one

Therapist protocol telephone support session one
Before the appointment:
Check the evaluation by the participant
Were there any questions or remarks
Check the decision letter (if possible)
Did the participant formulate a dysfunctional belief?
Start:
Mention that the support session is aimed at extra explanation and helping with the modules
How did it go, any difficulties?
Did participant manage to formulate a dysfunctional belief? If yes, compliment! Check whether belief is related to the participant. Use downward arrow technique when needed. If no, help participant choose one
It is possible to repeat the modules in case a participant wants to work on more than one belief
Any questions/remarks
Closing

Box 2. Therapist protocol for telephone support session two

Therapist protocol telephone support session two
Before the appointment:
Check the evaluation by the participant
Were there any questions or remarks
Check the assignment of module four
Did the participant choose a positive (dream) belief?
Check (if possible) assignment of module five
Did participant manage to assign characteristics to the belief?
In case the participant is at module seven, check the status of the behavioral experiment
Start:
Mention that the support session is aimed at extra explanation and helping with the modules
How did it go, any difficulties?
Did participant manage to formulate a positive/dream belief? If yes, compliment! When needed use CT based challenging techniques acquired through Mobile CT training
If needed help with assigning characteristics to positive/dream belief as well
Any questions/remarks
Closing

First a description of the website and Internet-based intervention was given. Further, we examined the total number of modules finished and defined adherence, in line with Hilvert-Bruce et al. (2012), as the proportion of patients that started the first module who completed the final module. We used the log data to extract the number of participants that finished each module. In addition, the total number of log-ins was derived from the log data. After each module participants filled in an evaluation about the perceived usefulness (very useful-not at all useful), perceived difficulty (very easy-difficult) and time spent on the module (less than 30 minutes-more than 120 minutes). This automatically derived information was used to examine the acceptability of the website to the participants. In addition, information on intervention drop-out per module and the qualitative experiences of therapists and participants were used to describe the difficulties with the website modules.

Therapist support

The total therapist support time per participant was calculated based on the information we received from the therapists. Therapist got paid based on support time in minutes. To calculate the total time per participant we added the time of the telephone sessions and time spent on reading and answering e-mails. In addition, the number of e-mails and telephone support sessions of each participant was gathered through the therapists and log data to assess the amount of therapist support needed in remitted, recurrently depressed patients.

Statistical analysis

The quantitative analyses were performed using SPSS version 20.0 and we considered 2-tailed *p* -values <.05 to be statistically significant. The user characteristics of participants that finished all modules where compared to participants who did not start at all and participants who followed at least one module out of all eight modules. Chi square tests were used to test differences in dichotomous variables and independent sample t-tests were applied to normally distributed continuous variables, for non-normally distributed variables the non-parametric Mann-Whitney U statistic was used. In addition, bivariate Pearson correlations were used to study associations

between user characteristics and the number of finished modules on the one hand, and the evaluated difficulty, usefulness, and time spent on modules on the other.

Results

User characteristics

Data of 129 participants was available that were allocated the Mobile CT. In Table 1, the baseline characteristics of the participants are presented. The baseline depression scores were low in all patients because our inclusion criterion was a remission status and a $HRSD_{17}$ score equal to or below 10. The depression scores on the IDS-SR_{30} fall into the category mild symptoms. Most participants were female (79.1%) and 41.1 % received higher education. Most baseline characteristics of participants that completed all modules did not significantly differ from participants that finished at least one module and the total group of participants randomized in to Mobile CT (all *p*'s >.05). However, a higher degree of the participants that did not start with Mobile CT (n=20) was unmarried, compared with participants that finished at least one module or all eight modules of Mobile CT (respectively, 60.0% versus 31.1% and 18.8%, *p* =.009). Further, participants that finished all eight modules had a somewhat higher score on baseline depressive symptoms measured with the IDS-SR_{30} than participants that started the first module but did not complete all modules (M=16.41, SD=11.3 versus M=15.21, SD=8.4, *p* =.036). In addition participants that did not finish the first module had a significantly higher score on depressive symptoms measured with the IDS-SR_{30} compared with participants that did finish the first module, but not all eight modules (M=17.95, SD=12.4 versus M=15.21, SD=8.4, *p* =.014). Finally, none of the user characteristics was associated with a higher number of finished modules and a higher number of total logins (all *p*'s >.05).

Table 1. Baseline demographic and descriptive characteristics of the study intervention population (N=129)

	Assigned to Mobile CT, but did not finish the first module (N=20)	Finished at least one module, but not all eight modules (N=45)	Finished all eight modules (N=64)
Age, mean (SD)	42.1 (12.1)	45.4 (10.4)	47.4 (10.7)
Female gender, no. (%)	16 (80.0)	37 (82.2)	49 (76.6)
Marital status, no. (%)			
Single	12 (60.0)	14 (31.1)	12 (18.8)
Married or cohabiting	7 (35.0)	24 (53.3)	43 (67.2)
Divorced	0 (0.0)	5 (11.1)	3 (4.7)
Widowed	0 (0.0)	0 (0.0)	2 (3.1)
Missing	1 (5.0)	2 (4.4)	4 (6.3)
Education, no. (%)			
Primary school	0 (0.0)	1 (2.2)	0 (0.0)
Secondary education	0 (0.0)	1 (2.2)	3 (4.7)
Vocational education	8 (40.0)	14 (31.1)	17 (26.6)
Pre-university education	1 (5.0)	0 (0.0)	1 (1.6)
Higher education	8 (40.0)	18 (40.0)	27 (42.2)
University	3 (15.0)	9 (20.0)	13 (20.3)
Missing	0 (0.0)	2 (4.4)	3 (4.7)
Previous episodes MDD, median (IQR)	4.0 (3.75)	4.0 (3.0)	4.0 (2.0)
Depressive symptomatology, $HDRS_{17,}$ mean (SD)	3.90 (2.7)	3.49 (2.8)	3.62 (2.9)
Depressive symptomatology, IDS-SR_{30}, mean (SD)	17.95 (12.4)	15.21 (8.4)	16.41 (11.3)

Note, SD=Standard deviation; MDD= Major Depressive Disorder; IQR= Interquartile Range; HDRS17= Hamilton Rating Scale for Depression; IDS-SR_{30}=Inventory of Depressive Symptomatology.

Website/ Intervention content

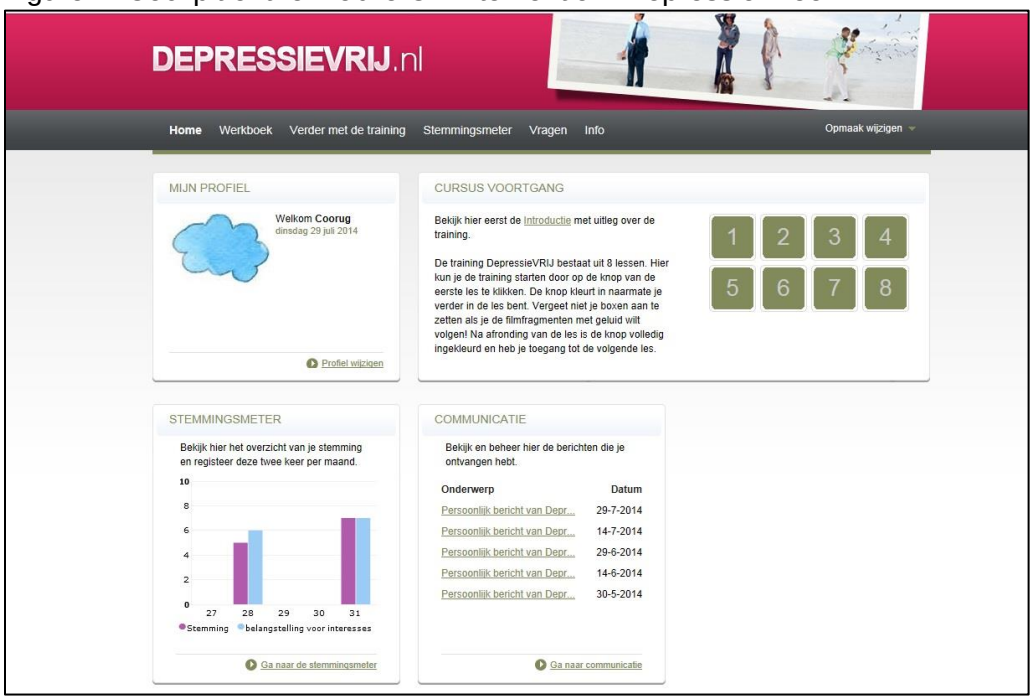
Each module has a fixed structure, with agenda setting, an evaluation of homework with automated feedback, the explanation of the rationale of each module and homework assignments. The content of all modules was based on a treatment manual (available on request from Claudi L.H. Bockting) (Bockting, 2009). All modules end with a short evaluation about the difficulty, usefulness and time spent on a module, and an option to save helpful exercises in a workbook. Further, in each module two videos can be viewed, one where a patient explains an exercise and one by an expert that explains the content.

The online intervention consists of three main components:

1) Identification and changing dysfunctional beliefs
2) Enhancement of positive experiences, by keeping a diary
3) Formulating relapse/recurrence prevention strategies

In the first module the main aim is the identification of negative thoughts. During the second module participants have to identify their dysfunctional beliefs, with help of a self-report questionnaire (Dysfunctional Attitude Scale) (A. N. Weissman, 1979). The participants were encouraged to examine whether they can explain what life circumstances contributed to the development of this specific belief. Module three consists of weighing the advantages and disadvantages of the dysfunctional belief, resulting in making a decision whether or not to continue examining the belief. A decision letter is written when the participant decides to change the dysfunctional belief. In module 4-7, multiple cognitive therapy based challenging techniques were used that focus on dysfunctional beliefs, such as identifying positive/dream beliefs and subsequently applying the multidimensional technique (Bockting & van Valen, 2009; Bockting et al., 2009). After formulating an alternative belief, in module seven participants practice with this new belief by making a flashcard. A behavioral experiment can be done as an option to reinforce the new belief. In modules 4-6 participants were asked to keep a diary of positive experiences and feelings. In modules 5-8, participants formulate specific relapse/recurrences prevention strategies. All information gathered throughout the modules was used to make a personal prevention plan in module eight, in which prevention strategies were included, such as visiting friends, calling someone, or exercising regularly.

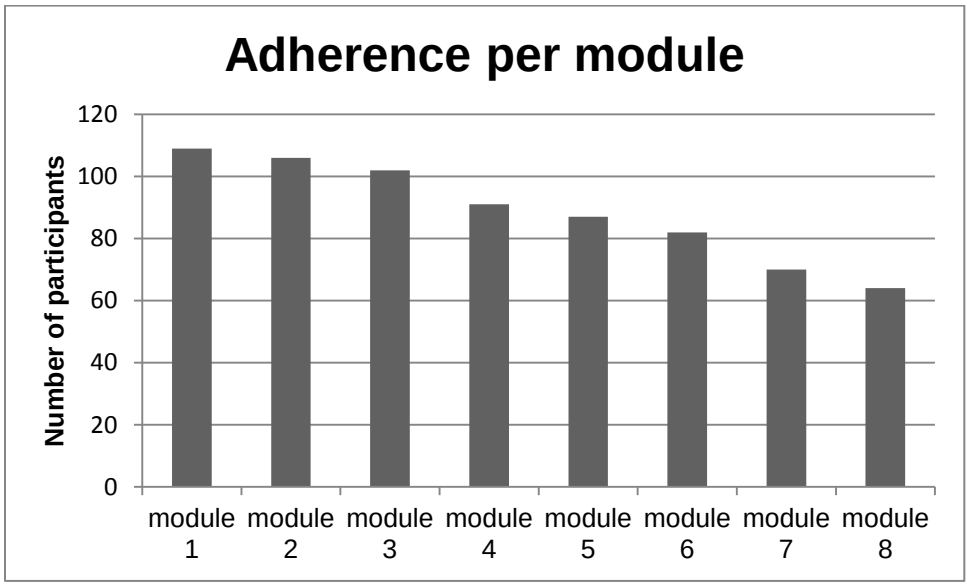
Figure 1. Cockpit of the Mobile CT intervention “Depressionfree”



Intervention usage/adherence

Of the 129 participants randomized to the Mobile CT group, 109 participants finished the first module and 64 participants finished all eight modules. The rate of participants that finished at least one module was 84.5% (109/129 participants). Full adherence (all eight modules finished) therefore was 58.7% (64/109 participants). Out of all participants, the average number of total logins was 25.3 (SD=22.7), in participants that finished at least one module but not all eight this was 18.84 (SD=16.9) and in participants that finished all eight modules this was 37.0 (SD=22.7). The mean of finished modules in participants completing at least one module, was 5.5 (SD=3.1). A somewhat higher part of the dropouts, occurred after module three (n=11), and module six (n=12). However, the intervention drop-out in Figure 2 shows a gradual decline over time of participants that completed each module.

Figure 2. Number of participants that finished the modules



Acceptability of the website based on evaluations

Figure 3 to 5 present the evaluations on usefulness, difficulty and time spent per module. Most participants rated the modules one to seven as useful and module eight as very useful. The ratings ‘not useful’ and ‘not at all useful’ were only given in module two to six and after module six were not given at all anymore, which might mean the modules after module six were more useful or that participants already dropped out after the previous modules or before filling in the evaluation. The same applies to the difficulty; most participants rated all modules as easy. The modules four, five and especially six were rated as difficult. This might explain the relatively high intervention drop-out after module six (n=12, 11%), instead of the initial rapid decline often demonstrated with Internet-based treatments (Eysenbach, 2005). However, participants did not rate module three as more difficult, while intervention drop-out was relatively high after this module as well. The evaluations on usefulness and difficulty of all modules were not associated with the number of finished modules (all *p*’s >.05).

Figure 3. Evaluation of usefulness per module

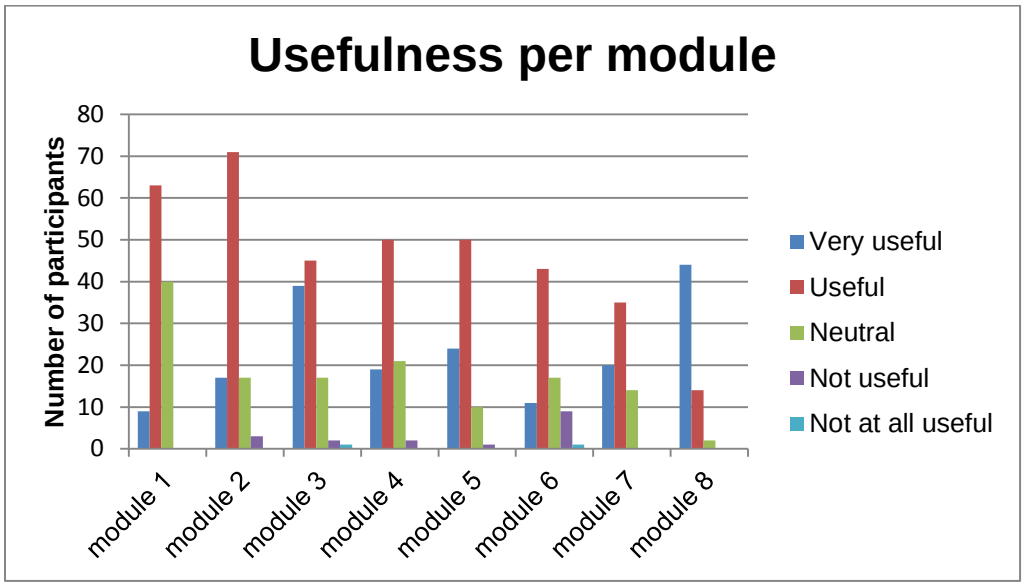
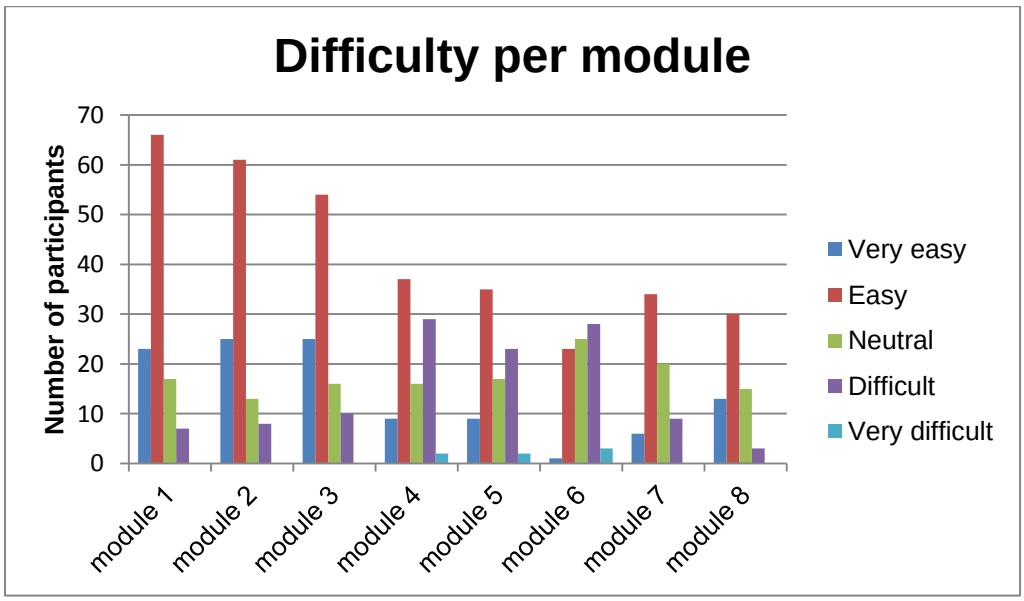


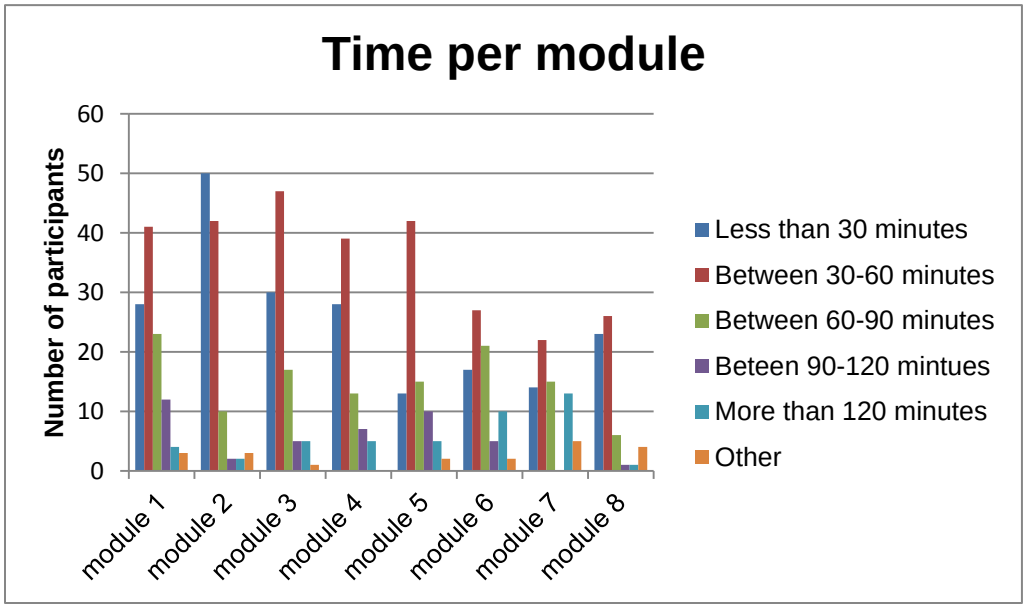
Figure 4. Evaluation of difficulty per module



Time spent per module

The time spent by participants per module mostly varied from 30 to 60 minutes. The amount of time was not associated with the number of finished modules as well (all *p*'s>.05). This indicates that the time spent on the modules was not related to adherence. In module six a significantly higher percentage of participants (longer than two hours: 9.2% in module six versus 0.9%-4.6% for other modules) spend a longer amount of time on the module than in the other modules (*p*<.05). The amount of time spent might therefore be related to the difficulty. Indeed statistically significant correlations of small to moderate size were found between difficulty of the module and the time spent on the module (with the exception of module one) (range of correlations per module *r*=.233-.381).

Figure 5. Evaluation of time spent per module



Qualitative analysis: experiences mentioned by therapists and participants

A few participants and one therapist voluntarily informed us about the experiences with the online intervention of Mobile CT. According to these participants, doing the intervention was helpful and easy to perform. Some participants mentioned the flashcard was very helpful.

Conversely also some difficulties were mentioned. In module three participants had to weigh the advantages and disadvantages of their dysfunctional beliefs and had to decide whether or not to continue work on challenging this rigid belief (Bockting & van Valen, 2009; Bockting, 2009). For instance for the belief: “people will appreciate me less when I make a mistake”, an advantage might be that such a person often delivers high quality work that will satisfy his/her employer. A disadvantage could be that this may costs a lot of time/energy and is stressful for the participant. During the telephone session after module two, one therapist noticed that some participants had trouble with selecting a specific dysfunctional belief out of the provided the list with examples of dysfunctional beliefs (Dysfunctional Attitude Scale) (A. N. Weissman, 1979). Further, some participants reported having trouble rating the characteristics of their dysfunctional belief. The therapist had the impression that drawing final conclusions based on this assignment was sometimes hard. While we expected formulating an extreme positive belief would be difficult, according to therapist and participants this was not the case. Conversely, some participants mentioned having difficulty with module six where participants had to draw conclusions based on their assigned scores. Focusing the therapist support sessions on these evaluations, and especially assisting with drawing conclusions, might be helpful for participants who have difficulties with this part. Also, a participant said: “what might help is to give a written example of how to draw conclusions” (received through personal communication). Although we used written and video based examples of how to perform the assignments in each module and added videos, with regard to drawing conclusions it might help to add an extra example of this. Further, according to the therapist, few participants carried out the behavioral experiment. This was an optional module that might not be necessary to include. In Internet-based therapies more help with setting up an experiment might be needed.

Therapist support uptake

The mean amount of total therapist support time per participant (telephone and e-mail) who completed at least one module of Mobile CT, was 21 minutes (SD=17.5). This is less than mostly reported in other studies where the total time is around 60 minutes (Marks et al., 2003; Proudfoot et al., 2004), and approximately 150 minutes for an Internet-based cognitive behavior therapy consisting of 10 email guided modules with additional 6 optional modules aimed at relapse prevention in partially remitted patients (Holländare et al., 2011). In Table 2 the therapist support uptake is presented for participants who finished at least one module of Mobile CT and participants who finished all eight modules. All participants were approached for the first telephone session with the therapist after they finished the second module and all participants that finished the fifth module were approached for the second telephone session with the therapists. Not all participants (n=66, 60.6%) were reached for the second therapist support session, because they did not finish the fifth module, did not respond to the invitation, refused a second session or thought it was not necessary. In participants finishing at least one module, but not all eight, the total therapist support time per participant was around 14 minutes (SD=17.3). In participants that finished all eight modules, total therapist support time per participant was around 24 minutes (SD=16.6). Participants completing the first module, but not all eight, did not initiate e-mail contact. In addition, 50% (32/64) of the participants who completed all eight modules initiated e-mail contact with their therapist with a mean frequency of 2.0 emails. E-mail contact was initiated by the participants, which implies that therapists did not initiated it by themselves.

Table 2. Therapist support uptake via telephone and e-mail contact

Modules finished	At least one, but not all eight, n=45	All eight, n=64
Second telephone support session, n (%)	12 (26.7)	31 (48.4)
E-mail contact, n (mean)	0 (0.0)	32 (2.0)
Total therapist support time (mean)	14 minutes (17.3)	23 minutes (16.9)

Discussion

In the current study we examined the usage of Mobile CT aimed at preventing relapse and recurrence in remitted, recurrently depressed patients. In our study, treatment adherence (58.7%) was comparable to the overall reported adherence to guided web-based interventions for health problems in the extensive meta-analysis by Richards and Richardson (2012) with an adherence rate ranging from 65.2%-72%. Remitted participants in general finished a high number of the modules (M=5.5, SD=3.1) and frequently logged in (M=25.3, SD=22.7). This might indicate that participants also logged in after finishing all modules, as was intended by the developers. Unfortunately this could not be checked because data on the exact login times was not available.

Most participants in our study were female, highly educated and married or cohabiting, which is comparable to other studies on web-based interventions aimed at depressed individuals (e.g. Andersson et al., 2005; Holländare et al., 2011; D. Kessler et al., 2009). In contrast to previous findings, characteristics such as education level and depressive symptom levels were not associated with intervention completion in our sample (Christensen et al., 2009; Warmerdam, van Straten, Twisk, & Cuijpers, 2013). However, the participants that did not start with the intervention were more often unmarried than participants that finished at least one or all eight intervention modules. In addition, depressive symptoms in participants that finished at least one module, but not all eight modules, were lower than depressive symptoms in participants that did not finish the first module or finished all eight modules.

Remarkably, the therapist support in our study was minimal while adherence was comparable to other studies on guided Internet-based treatments, using more guidance time. Intervention drop-out was relatively low and steady over time and did not demonstrate any specific patterns, such as initial rapid decline (Eysenbach, 2005). Treatment drop-out could be an indication of a negative effect of treatment, such as worsening of symptoms and nonresponse. Examination of drop-out is therefore highly important (Rozental et al., 2014). The uptake of therapist support in our study was very low, with only 21 minutes in total. Other studies report a mean support time of 60 minutes (Marks et al., 2003; Proudfoot et al., 2004), and approximately 150 minutes for

an Internet-based cognitive behavior therapy aimed at relapse prevention in partially remitted patients (Holländare et al., 2011). Given that adherence was comparable to other guided Internet-based interventions and face-to-face interventions (e.g. Hilvert-Bruce et al., 2012; D. Richards & Richardson, 2012), this might suggests that even with less support, an Internet-based treatment might be effective. Interestingly, in our study a low number of participants responded to our request to schedule a second therapist support session by telephone. In addition, a low number of emails was sent by participants to their therapist. This is in accordance with previous research demonstrating the low number of participants that initiated contact when this was not pre-scheduled (Marks & Cavanagh, 2009). In addition, it might also be that participants knew that support would be minimal and acted accordingly (D. Richards & Richardson, 2012). The low therapist support time might be an effect of the specific training therapist received in applying blended care including the restricted time frame for the telephone support sessions. Alternatively, since we included participants that were remitted, less support time is needed to complete the modules compared with guidance in acutely depressed patients. Treatment needs could fluctuate dependent on the depression stage (Guidi et al., 2011), and during remission participants may have different treatment needs than during a depressive episode. Currently, there is a lot of uncertainty with regard to the required level and type of support that is needed in Internet-based psychotherapies (Donker et al., 2009). For example, recent research demonstrated that support by receptionists, nurses, lay people, research coordinators, administrative staff, or technicians might be as effective as support by a mental health professional (D. Richards & Richardson, 2012; Robinson et al., 2010).

Most participants rated the modules as useful and easy in the evaluations at the end of each module. Finishing the modules took around 30-60 minutes. This indicates that Mobile CT might be an acceptable treatment for most participants. The relatively high adherence rates might be caused by the intervention being developed in such a way that each module could be completed within approximately 20 minutes and participants could choose whether to read information, watch videos and do certain assignments such as the behavioral experiment. However, one therapist did notice that some participants experienced difficulties with the some aspects of the specific

challenging techniques (drawing conclusions). Whether this finding applies to other Internet-based treatments using this technique is unknown and more research will be needed to examine this. These results on intervention uptake might be limited to remitted patients.

Limitations and future directions

Unfortunately, no information was available in the log data on the date and amount of time spent by participants per module. This is an important limitation of this study. However, participants did fill in the amount of time spent per module in the evaluation at the end of each module. While we advised participants to finish around one module per week, we were not able to check whether they actually did this. However, from our previous study we do know that a high proportion (80%) of the completers finished the modules within three months (Kok et al, *under review*). However, participants did fill in the amount of time spent per module in the evaluation at the end of each module. Gathering information on the time needed to finish modules is relevant because there are indications that a higher intensity of treatment is associated with a higher effect size of face-to-face psychotherapy (Cuijpers, Huibers, Ebert, Koole, & Andersson, 2013). Whether this also applies to Internet-based psychotherapies, is unknown. Further, we instructed participants to repeat modules as often as they wanted. However, because information on the dates of logins was not available, it is unsure how often it occurred that participants repeated modules. Therefore, when designing an Internet intervention it is very important to have a clear idea about what to put into the log data before the start of the study. In addition, the information with regard to the reported difficulties with multiple CT based challenging techniques, was based on only a small proportion of participants and on experiences of one therapist. The therapist and participants mentioned these difficulties to the researchers on their own initiative. Because no standardized questionnaire was used to assess the experience with the challenging techniques, these findings might not be generalizable.

Further, the main aim of this study was to gain insight in the use of an Internet-based relapse prevention treatment in remitted participants. Future comparative and or randomized controlled studies are needed to replicate our findings.

Another limitation, to this and a most other studies on Internet-based therapies, is that there is no universally accepted measure of adherence to Internet-based treatments and multiple definitions of adherence exist, varying from frequency of logins, time on website and number of modules finished (Christensen et al., 2009). Comparing adherence rates between studies on Internet-based treatments is therefore complex. Defining and using a single universal definition is advised to better understand which factors influence treatment outcome. In addition, patients could adhere to the Internet-based intervention, while they might not adhere to therapist support and monitoring by text messages and e-mails. It would be important to differentiate between these different types of drop-out to examine what factors impact on treatment outcome.

Further, all participants were recruited within the context of a randomized controlled trial and volunteered to participate in a study on Mobile CT. Participants were between the ages of 18 and 65, in remission of at least two previous depressive episodes. Therefore, it is unclear whether our results can be generalized to other populations. Finally, during the current study no information on the mood monitor was present and therefore its usage was not yet examined.

Conclusion

We demonstrated that the therapist support time in remitted recurrently depressed patients was low while intervention adherence of participants was relatively high. In addition, participants and therapists rated Mobile CT overall as usable, acceptable and user-friendly. Our results are a first indication that during remission, an Internet-based treatment as Mobile CT might be a feasible form of continued care that prevents return of symptomatology and relapse and recurrence in this chronic disease. However, replication is warranted. This relapse prevention strategy might warrant implementation in routine practice after consolidation of our first positive findings on depressive relapse (Kok et al., under review). Internet-based therapies increasingly become an integral part in mental health care and further studies on its uptake helps to obtain insight in how to offer these treatments optimally in daily clinical practice.

Chapter 10

General Discussion

In the present chapter the main outcomes are described in light of previous research findings, and the implications for the vulnerability-stress and scarring hypotheses will be discussed. Further, limitations, future directions and clinical recommendations will be provided. In part one, we examined the associations of childhood adversity, minor life stress sensitivity, chronic somatic illness and personality disorder with the course of depression. In part two of this thesis we examined treatment strategies aimed at the prevention of relapse, including an Internet-based Cognitive Therapy (CT) with monitoring by text messages and minimal therapist support by telephone (Mobile CT).

Part I

Premorbid vulnerability: childhood adversity

A premorbid vulnerability to recurrent depression might be present even before the first onset of depression. Therefore, we examined whether the premorbid vulnerability factor childhood adversity was associated with the return of depressive symptoms after remission, and whether previous episodes impacted this association. In contrast to our expectancy, we did not find evidence for this, while other studies demonstrated childhood adversity to predict relapse, even in comparable populations of recurrently depressed patients (Lok et al., 2013; Nanni et al., 2012). We therefore cautiously concluded that childhood adversity does not always predict the return of depressive symptoms in this remitted stage.

According to the vulnerability stress hypothesis, certain individuals are more vulnerable to life stress and therefore more prone to depressive relapse. We examined whether childhood adversity was associated with heightened minor stress sensitivity and therefore triggers subsequent depressive symptoms after remission in recurrently

depressed patients. Life stress sensitivity was operationalized as the reported intensity and frequency of dependent and independent minor (daily) life stress. Independent life stress is externally generated (e.g. an accident happening to a friend), dependent life stress on the other hand, is internally generated, (e.g. having too many social obligations). We found that childhood adversity was not significantly associated with higher life stress sensitivity and, therefore, not associated with depressive symptoms at follow-up. This adds to the mixed findings in previous research, where two out of the three studies demonstrated that the experience of childhood adversity was associated with higher stress sensitivity which significantly heightened the risk of depression onset (Comijs et al., 2007; LaNoue et al., 2012; McLaughlin et al., 2010).

However, we uniquely contribute to the research into the association between childhood adversity and stress sensitivity by looking at this association in, specifically, remitted recurrently depressed patients. Our results suggest that childhood adversity is not always associated with higher stress sensitivity, and by association, the return of depressive symptoms after remission. This is in accordance to the diathesis-stress model proposed by Patten (2013), in which the interaction between exposure to life stress and the degree of vulnerability is said to be changeable and therefore leads to fluctuations in depressive symptom levels over time. In line with this, van der Werf *et al.* (2006) and Kaptein *et al*. (2007) found that a pile-up of life stress caused fluctuations in mood. In patients with recurrent depression, episodes occurred more often and were shorter than the episodes in patients with first onset of depression. Ormel, Oldehinkel and Brilman (2001) suggested that this is caused by a general vulnerability in recurrently depressed patients, making them more susceptible to life stressors. Whether this vulnerability is present before the first episode of depression remains unknown.

The participants in our study experienced a median of four previous episodes, which might have left scars in terms of stress sensitivity, dominating a possible influence of childhood adversity. However, stress levels before the first onset of depression were not measured, and therefore no decisive statements regarding scarring can be made. Accordingly, it might be methodologically difficult to detect an influence of childhood adversity on stress in this remitted recurrently depressed patient group.

Minor life stress

An association between the exposure to life stress and the development of subsequent depression is consistently documented (Hammen, Kim, Eberhart, & Brennan, 2009; R. C. Kessler et al., 1997; Monroe & Harkness, 2005). However, the influence of life stress on depression changes dependent on the number of previous episodes (Kendler, Thornton, & Gardner, 2000; Stroud, Davila, Hammen, & Vrshek-Schallhorn, 2011), and in the presence of previous episodes it is unknown which type of life stress triggers another episode. It is feasible to consider that episodes will occur automatically and independently of environmental stress in time (Post, 1992). Therefore we examined whether minor life stress was associated with the return of depression in recurrently depressed patients, and if previous episodes impacted this association.

We found the reported intensity of dependent and independent minor life stress to be predictive of subsequent depressive symptoms after remission in recurrently depressed patients (chapter two). We found no evidence for the scarring hypothesis, given that the number of previous episodes was not associated with heightened life stress sensitivity. However, we examined a highly recurrent patient group, and scarring could have already taken place following earlier episodes. Our findings underscore previous research, that minor life stress is associated with depressive relapse (Bockting et al., 2006; Harkness et al., 2006; Lenze et al., 2008; Monroe et al., 1996; Ormel et al., 2001; ten Doesschate et al., 2010). Preventive treatments that target dealing with, specifically, minor life stress may therefore be effective in preventing further episodes.

Previous research has demonstrated that increasing numbers of minor life stressors predicted depressive relapse/recurrence only in the treatment as usual condition, but not in the preventive Cognitive Therapy (CT) condition (Bockting et al., 2006). It has been suggested that Preventive CT might have disrupted the influence minor stress might have had on reactivating depressive thinking patterns (Bockting et al., 2006). This indicates that dealing with minor stress might be modifiable with treatment (Bockting et al., 2006; ten Doesschate et al., 2010). In addition, dealing with life stress is mentioned as a treatment ingredient in mindfulness based cognitive therapy and well-being cognitive therapy as well (G. A. Fava et al., 1994; G. A. Fava et al., 1996; G. A. Fava et al., 1998; G. A. Fava, Rafanelli et al., 1998; G. A. Fava et al.,

2004; Ma & Teasdale, 2004; Segal et al., 2010; Teasdale et al., 2000). It might even be that these interventions are effective because of their influence on the experience of life stress instead of cognitions, which is the original model of cognitive therapy (Beck, 1967). Understanding the underlying mechanisms of treatment efficacy and establishing what works for whom, may improve preventive treatment strategies. This might help patients who respond insufficiently to existing treatments and lengthen treatment effects.

Chronic somatic illness

While research demonstrated major chronic life stress to be related to a higher number of prior episodes of depression (Monroe, Slavich, Torres, & Gotlib, 2007a), few studies have examined the influence of chronic life stress on the course of depression prospectively. Therefore, we examined whether the presence of chronic somatic illness, a chronic life stressor, was associated with prospectively assessed depressive relapse and a longer time to remission.

In our first systematic review (chapter three), we found no association between higher relapse rates and the presence of a chronic somatic illness. In the second systematic review, we meta-analytically evaluated time to remission. The pooled outcome of all five studies did not indicate a difference in time to remission between individuals with versus without a chronic somatic illness. These findings contrast with recommendations of international clinical practice guidelines of treatment of MDD and experts in the field, stating that depressed patients with comorbid chronic somatic illness need longer depression treatment (American Psychiatric Association, 2010; Evans et al., 2005; National Institute for Health & Care Excellence, 2010). Based on our findings, a specific focus on this comorbid group with regard to preventive treatments appears not to be justified until more longitudinal studies have been done that indicate the opposite. Therefore, for now, recommendations for long-term treatment should not be based on the presence of a chronic somatic illness specifically.

Personality disorder and cognitive vulnerability

The presence of personality disorder is associated with a longer time to remission and an increased risk of depressive relapse (Grilo et al., 2010; Newton-Howes et al., 2006; Skodol et al., 2011). This might be explained by the presence of personality disorder being perceived as a chronic life stressor activating cognitive vulnerability. Whether an association between personality disorder and cognitive vulnerability is present in remitted recurrently depressed patients is unknown. In our study, exactly half of the remitted recurrently depressed patients indicated the presence of a personality disorder (50%). This is in agreement with other studies demonstrating a high prevalence of personality disorder in depression (48%-52%) (e.g. Farabaugh et al., 2007; Grilo et al., 2010; Pilkonis & Frank, 1988; Sato et al., 1994; Skodol et al., 2011). In accordance with the scarring hypothesis, especially after exposure to multiple depressive episodes, depression might alter personality (Hirschfeld & Klerman, 1979; D. N. Klein et al., 2002; Klerman et al., 1987; Ormel et al., 2001).

Post-hoc, we found no association between the number of previous episodes and 1) the presence of personality disorder, 2) the number of personality disorders, and 3) the dimensional score on personality disorder (i.e., continuous levels of pathology; (Durbin & Klein, 2006; Melartin et al., 2010; Samuel et al., 2011) in our study. Therefore, no indication for scarring was found. However, no information on personality disorder before the first onset of depression was present and no decisive statements regarding scarring can be made.

We demonstrated that the presence of personality disorder (dichotomous and continuous) was associated with higher levels of dysfunctional beliefs, cognitive reactivity and rumination, even after controlling for depressive symptoms. Of all cognitive vulnerability variables, dysfunctional beliefs showed the strongest association with personality disorder, irrespective of the type of personality disorder. This might indicate cognitive vulnerability as epiphenomena of personality disorder (Craighead et al., 2011; Otto et al., 2007). Nevertheless, cognitive vulnerability, and especially dysfunctional beliefs, may serve as preventive treatment aims in recurrently depressed patients. However, whether an association between dysfunctional beliefs and personality disorder leads to an increased risk of relapse is yet unknown.

Part II

Preventive psychological treatments

We conducted a meta-analysis that aimed to examine whether preventive psychological treatments are more effective in reducing relapse compared to Treatment as Usual (TAU) and Antidepressant Medication treatment (ADM) (chapter six). TAU could consist out of routine clinical management, assessments only, no treatment and waiting-list control with unrestricted access to TAU. The psychological interventions that were meta-analytically examined were diverse and consisted of Internet-based treatment, booster sessions, group-, and individual treatment. A systematic search generated randomized controlled trials on Cognitive (Behavioral) Therapy (C(B)T), preventive CT, interpersonal therapy and Mindfulness Based CBT) (MBCT). No randomized controlled trials on other psychotherapies such as, problem-solving therapy and psychodynamic therapy were found and included in our meta-analysis.

Preventive psychological interventions were effective in reducing relapse over a mean follow-up of two years versus TAU and ADM treatment with a relative risk of 0.64 and 0.81, respectively. These results are an extension to previous research which demonstrated that C(B)T, including MBCT, after remission might be equally effective in reducing the risk of depressive relapse as ADM treatment and more effective than TAU (Guidi et al., 2011; Kuyken et al., 2008; Piet & Hougaard, 2011; Vittengl et al., 2007). Further, we found the effectiveness of the psychological interventions to enhance when patients received acute phase treatment. This might be caused by the long-term preventive effect of acute phase CBT on depressive relapse (Cuijpers et al., 2013).

Previous research demonstrated that the effectiveness of mindfulness based CBT and preventive C(B)T was limited to patients with a higher number of previous episodes (Bockting et al., 2005; Bockting et al., 2009; Ma & Teasdale, 2004; Piet & Hougaard, 2011; Stangier et al., 2013; Teasdale et al., 2000; Vittengl et al., 2007). An explanation for this might be that preventive treatments target internal (meta-cognitive) depressive associations that develop during the course of depression (Beshai et al., 2011). Our findings did not demonstrate this. Preventive psychological interventions were effective irrespective of the number of previous episodes. Current national and international

clinical practice guidelines state that prevention of relapse with preventive C(B)T or MBCT is especially effective in patients with three or more previous episodes and that the number of previous depressive episodes should be taken into account when deciding on relapse prevention (American Psychiatric Association, 2010; Guidi et al., 2011; National Institute for Health & Care Excellence, 2010; Piet & Hougaard, 2011; Spijker et al., 2013; Vittengl et al., 2007). However, our results suggest that prevention of relapse treatment could be advised to all patients, irrespective of their depression history.

Mobile Cognitive Therapy, short-term effects and website usage

An Internet-based cognitive therapy (CT) combined with monitoring by text messages (Mobile CT), and minimal therapist support (e-mail & telephone), was developed, piloted and evaluated in our randomized controlled trial. We demonstrated that Mobile CT significantly reduced depressive symptoms levels, measured with the Inventory of Depressive Symptomatolgy (IDS-SR_{30}), over three months of follow-up compared to TAU in participants fully remitted from recurrent depression (Cohen's d=0.44; chapter eight). TAU could consist of multiple types of treatment, such as ADM treatment, maintenance or continuation therapy by a psychologist or psychiatrist, or no treatment at all. There were no restrictions to the type of TAU. Controlling for specific TAU and the number of previous episodes did not materially change the results. Importantly, the effect was even larger in participants that finished a higher number of modules (≥ 5). This finding fits previous research on acute treatment of anxiety and depression, demonstrating that the effectiveness of Internet-based therapies depends on treatment adherence (Christensen et al., 2009).

In chapter nine, the adherence and acceptability of the online intervention was examined to establish, and to possibly increase efficiency, the efficiency of Mobile CT. Of all 129 participants, 109 participants finished at least one of all eight modules of Mobile CT (84.5%) and 64 participants finished all eight modules (49.6%). In line with Hilvert-Bruce et al. (2012), adherence was defined as the proportion of patients that started the first module who completed the final module. Adherence was therefore 58.7% (64/109), which was comparable to the 65.2%-72% found in other studies on

guided Internet-based psychotherapies (D. Richards & Richardson, 2012). Given that the total therapist support time per participant in our study was lower (21 minutes) than found in other studies in depressed patients and patients in partial remission of depression (60-150 minutes) (Holländare et al., 2011; Marks et al., 2003; Proudfoot et al., 2004), this suggests that adherence to an Internet-based treatment can be high with less therapist support.

Overall, participants rated Mobile CT as an acceptable treatment in terms of difficulty, time spent per module and usefulness. However, one therapist mentioned that a small proportion of the participants experienced difficulties with using multiple CT, based challenging techniques. These short-term effects indicate Mobile CT added to TAU, an effective and acceptable way of treating depressive symptoms after remission in highly recurrent patients.

It is very plausible that not all patients need face-to-face preventive therapy. Although there are first indications that the effects of guided self-help interventions (blended care), such as Internet-based psychotherapy, might be comparable to face-to-face psychotherapy for acute treatment, this is less clear in patients that seek help in specialty care (Andersson et al., 2013; Cuijpers, Donker, van Straten, Li, & Andersson, 2010). Therefore, future research should examine whether Internet-based preventive therapies, such as Mobile CT, are equally effective as face-to-face preventive therapies.

Main limitations and implications for further research

In addition to the limitations already mentioned in the separate chapters, findings have to be interpreted in light of some key limitations of the studies.

Participants: While it is an advantage to study patients at high risk of relapse to determine which risk factors influence the return of depression, exposure to previous episodes of depression might also make it hard to detect an influence of premorbid vulnerabilities such as childhood adversity. Therefore, to truly grasp the influence of premorbid vulnerability on depression onset and relapse, participants should be longitudinally followed from before the first onset of depression. Further, with regard to the generalizability of our results, the participants recruited within the context of our

RCTs were seeking help for the prevention of depressive relapse. Therefore this sample might not reflect the whole population with recurrent depression. In addition, our inclusion criteria (i.e., highly recurrent group, between age of 18-65 years, fluent in Dutch) may also affect the generalizability of the results. Finally, with regard to the studies performed in our RCTs we should keep in mind that most participants that drop-out of prospective follow-ups are the ones with poorer outcomes (Lee, 2003). Leaving these patients out of the analyses may cause bias and, because not all data are used, reduced statistical power. Fortunately, as long as 'missingness' of data, i.e. due to drop out, can be predicted from available data (the missing at random (MAR) assumption holds), both multiple imputation and linear mixed models including all patients yield unbiased results. It is therefore not surprising that these techniques are frequently used in amongst others randomized controlled trials (White, Horton, Carpenter, & Pocock, 2011). It is, however, impossible to prove that the MAR assumption holds and this forms a limitation of these techniques. Notably, after Multiple Imputation (chapter two & five), analyses including patients with complete information for all relevant variables (complete case analyses) revealed comparable results.

Assessments: The studies performed in the context of our RCTs (e.g. chapter two & eight) had a limited follow-up time of three months and a relatively small sample size which might have lowered the chance of detecting an effect. In addition, participants were remitted at the start of the study which could have made finding an effect difficult. Replication of these findings with a longer follow-up is required before firm conclusions can be drawn. With regard to the difference in depressive symptom levels over three months after remission in the TAU and Mobile CT added to TAU groups (chapter eight), the effect might seem small; however during the remission even small increases in depressive symptoms are predictive of relapse (Judd et al., 1998).

Regarding the studies on childhood adversity and chronic somatic illnesses (chapter two, three & four), it is questionable whether all types of chronic somatic illnesses and childhood adversities have the same impact on depression. Future large-scale studies are needed to examine this and differentiate between different types of somatic illnesses and childhood adversities. An interesting question for future research might be whether the prognosis of depression could deteriorate when somatic illness

progresses. In addition, a wide variety of other types of childhood adversities and somatic illnesses were not assessed but could impact the course of depression.

Further, we used self-report questionnaires to assess childhood adversity, minor life stress and personality disorder. With regard to the assessment of life stress (chapter two), self-report is said to lead to interpretative biases by patients and it lacks contextual information (Alloy et al., 2010). In addition, assessing personality disorder using self-report is prone to over-diagnosis (Hyler et al., 1990). However, in chapter five, this was adjusted for in order to increase agreement with the SCID-II (van Velzen et al., 1999). The rates of personality disorder in our study were comparable to the rates of personality disorder assessed using the SCID-II (Farabaugh et al., 2007; Sato et al., 1994). However, using interviews in the future is preferred.

Further, the number of previous episodes of depression was retrospectively assessed with the SCID-I and recall could have been affected by memory bias. In chapter two and eight depressive symptoms were assessed using the IDS-SR_{30} at fixed time points, and therefore, variations in-between could have been missed. Regarding recurrent depression, it will be of relevance to know whether these individual pathways to depression change dependent on the history of depression. Finally, variables other than the ones we studied, could be of importance. In light of the vulnerability stress model, information on genes, family history, coping and mastery could all help throwing light on the pathways to poor depression outcomes. Future studies should include important risk factors and their interactions to prevent the isolation of factors.

E-Health: In chapter eight, it is unsure whether the difference in depressive symptom levels over three months after remission between the Mobile CT added to TAU group and the TAU group, was caused by Mobile CT. Therefore, we do not know which non-specific factors might play a role. In addition, we do not know whether it was the intervention part of Mobile CT, the therapist support, the mood monitoring or a combination that caused the effect. In e-mental health, often multiple technologies are combined and the examination of the effectiveness of separate parts of interventions might help deciding on which treatment strategy to apply.

An additional complicating factor for our usability study (chapter nine), is that patients could drop-out of the experimental condition, the trial assessments, the

therapist support and mood monitoring, as well. It would be important to differentiate between these different types of drop-outs to examine which factors influence treatment outcome. Further, no information was available in the log data on the date and the exact amount of time participants spent per module. However, participants did estimate the amount of time spent per module in the evaluation at the end of each module. While we advised participants to finish around one module per week, we were not able to check whether they actually did this. However, we do know that a high proportion (80%) of the completers finished the modules within three months (chapter eight). Gathering information on the time needed to finish modules is relevant because there are indications that a higher intensity of treatment is associated with a higher effect size in face-to-face psychotherapy (Cuijpers, Huibers, Ebert, Koole, & Andersson, 2013). Therefore, when designing an Internet intervention, it is very important to have a clear idea about what information is needed to automatically derive out of the log data before the start of the study.

Clinical implications

In line with previous findings and clinical practice guidelines of MDD treatment, CBT, preventive CT, and MBCT could be recommended to (partially) remitted recurrently depressed patients (American Psychiatric Association, 2010; National Institute for Health & Care Excellence, 2010; Vos et al., 2004). In addition, interpersonal therapy could be advised as well, as long as it is continued (e.g. monthly), after remission (chapter six). Further, Internet-based preventive therapies, such as Mobile CT, might be an effective way of relapse prevention.

Implementation of E-mental health interventions in clinical practice

Instead of replacing face-to-face therapies, Internet-based treatments like Mobile CT could be part of a blended care approach. Offering blended care options to patients broadens the options when matching treatment strategies to treatment needs. After the detection of depressive relapse, other types of treatment might be added, for example, supported Internet-based C(B)T face to face C(B)T, interpersonal therapy or ADM treatment. In addition, dependent on the depression phase and patient preference, one could vary the amount and type of therapist support. Face-to-face contacts might be added or reduced and other technologies such as the Internet, text messages and telephone support might be considered.

Patients can have a more active and directing role in e-mental health interventions, because they mostly choose the time and place. Often patients will come up with questions themselves and the role of the therapist will be to motivate and help patients finish their exercises (Blankers et al., 2013). Offering support by telephone or with text messages means quickly getting to the core of the problems and requires structured and transparent communication because of the lack of non-verbal cues.

In previous research, barriers to the implementation of e-mental health therapies were found in the selection and training of individuals willing to work in a mental health care environment with increased availability of resources, such as telephone and the Internet (D. A. Richards et al., 2006). A lot of organizational and practical concerns were found. For example, mental health professionals thought all contacts with patients had

to be with established professionals. However, patients themselves were satisfied with a skilled case manager. Addressing and understanding barriers, such as willingness to incorporate new strategies, technical knowledge, cost and time investment, role adjustment, and skepticisms will help implementation.

What works for whom

Importantly, everyone who experienced one episode of depression is at risk of depressive relapse. Therefore, the prevention of relapse in recurrent depression is highly important for remitted individuals. Also, patients vary in their treatment needs. It is thus extremely relevant to match the best treatment to patients in order to reduce the burden of depression.

Patients with an ultra-high risk of depressive relapse might need a different treatment strategy than patients with a high risk of depressive relapse. For example, research demonstrated that in patients with less than five episodes, psycho-education led to the same reduction in risk of relapse as preventive CBT (Stangier et al., 2013). However, in patients with five or more previous episodes, preventive CT resulted in lower relapse rates than psycho-education. The preventive CT was focused on, amongst others, the modification of dysfunctional cognitions and beliefs, behavioral experiments and stress testing. In another study, MBCT was as effective as TAU and cognitive psychological educations, which consisted of the same ingredients as MBCT but without the “experiential cultivation of mindfulness through meditation practice” (pp 278) (J. M. Williams et al., 2014). However, MBCT was the more effective treatment in patients exposed to more childhood adversity (J. M. Williams et al., 2014). While replication is needed, this might indicate that more specific treatment is required when patients are more vulnerable to depressive relapse (i.e. unstable remission, more previous episodes, possibly childhood adversity) (American Psychiatric Association, 2000; Bockting et al., 2005; Burcusa & Iacono, 2007; G. A. Fava et al., 2004; Judd et al., 1998; Mueller et al., 1999; Solomon et al., 2000; ten Doesschate et al., 2010).

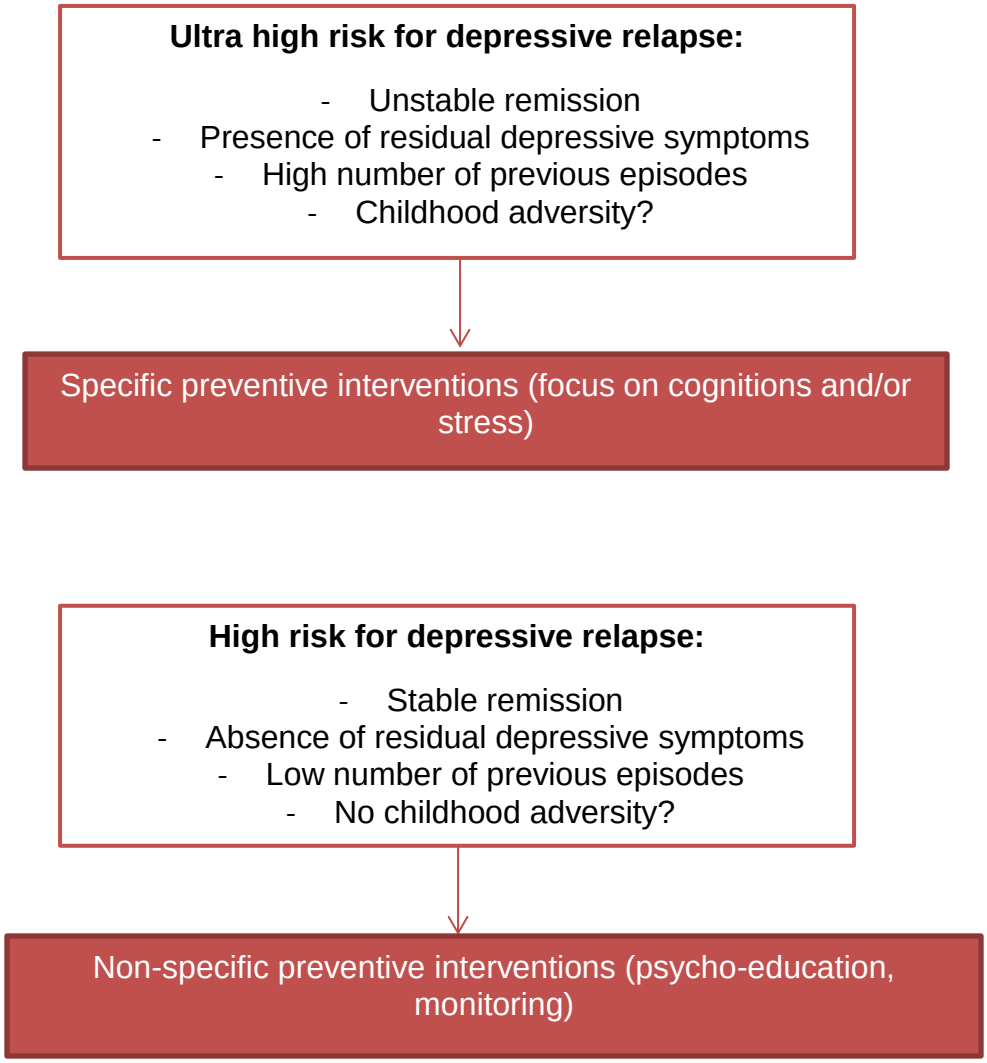
Applying personalized prevention strategies, with the choice of treatment depending on the presence of vulnerability to depressive relapse, might increase the effectiveness of treatment. Current specific preventive interventions like preventive CT

and MBCT might be implemented to prevent depressive relapse when an ultra-high risk for depressive relapse is present, whereas a less specific intervention, such as psycho-education or perhaps even only monitoring of mood, might be enough to prevent relapse when the risk of depressive relapse is relatively less high.

In Figure 1, a model for future research on treatments aimed at the prevention of relapse is proposed, based on the presence of prognostic factors (e.g. number of episodes, residual symptoms). This model is intended as a research model to examine whether risk factors can be used to match a treatment to individuals. The model presented here is not intended to be used as a decision- or prediction tool. Furthermore, this model does not attempt to account for several other potentially important factors. While some of these risk factors (number of episodes, residual symptoms), are extensively studied, others (childhood adversity) need more research.

In addition, we suggest that the type of treatment should match the current stage of the disease. For example, during remission there is more room for training the recall of positive experiences, and the need for therapist support is suggested to be lower during remission than during the acute and subsyndromal phase of depression. In this case, a minimally supported Internet-based treatment may benefit remitted patients while depressed patients might need a different type of approach. Finally, it is questionable whether the response to a treatment will remain stable across different episodes of depression (Simon & Perlis, 2010). For example, response to a specific antidepressant medication during a first episode is no guarantee for response to the same antidepressant during a fourth episode. Everything we experience changes us as a person (Kendler et al., 2011), and pathways to depressive relapse might change with each consecutive episode. This fits a dynamic treatment approach, where the choice of treatment is not predetermined but depends on the needs of individuals and the disease stage (Guidi et al., 2011), and also previous experiences.

Figure 1. Model for future research on preventive interventions



In conclusion

Personalized treatment is an important challenge in mental health care. Future studies are needed to further examine the (possibly fluctuating) risks for depressive relapse and examine the effects of preventive treatment strategies for patients with an ultra-high risk for depressive relapse and a high risk for depressive relapse.

The development and evaluation of new treatment strategies, such as Mobile CT, broadens the options in relapse prevention treatments. The next challenge could be to enhance matching treatments to individuals at different stages of MDD.

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Nederlandse Samenvatting

Depressie is een veelvoorkomende aandoening, welke gepaard gaat met veel leed voor mensen zelf en hun omgeving. Voor veel mensen is een depressie geen eenmalige, maar een terugkerende aandoening. De titel van dit proefschrift "*Under Pressure"* verwijst naar mensen met een hoog risico op depressieve terugval die behandeling nodig hebben om terugval te voorkomen. De vraag is echter, wat zijn deze risicofactoren en hoe voorkomen we terugval? Dit proefschrift is opgedeeld in twee delen. Het eerste deel richt zich op het onderzoeken van risicofactoren voor terugval en het tweede deel richt zich op behandelstrategieën ter voorkoming van terugval, waaronder een nieuwe behandeling aangeboden via Internet en de mobiele telefoon.

Inleiding deel 1

Om behandeling zo goed mogelijk af te stemmen op patiënten, en mogelijke risicogroepen te onderscheiden, is het van groot belang om inzicht te krijgen in risicofactoren van terugval bij depressie.

Een kwetsbaarheid voor recidiverende depressie zou al kunnen bestaan voor het eerste ontstaan van depressie, in dit proefschrift noemen we dit een premorbide risicofactor. Bij premorbide risicofactoren kan men denken aan nare ervaringen in de kindertijd, zoals het overlijden van een ouder of seksueel misbruik.

Volgens de *vulnerability-stress* hypothese, kunnen premorbide risicofactoren tot een depressie leiden omdat ze mensen gevoeliger maken voor levensstress. Onderzoek toont aan dat grote levensstressoren, zoals de dood van een geliefde, vaker geassocieerd zijn met het ontstaan van een eerste depressie, dan met de terugkeer van een depressie. In plaats daarvan wordt alledaagse levensstress, zoals ruzie met de buren, vaker geassocieerd met de terugkeer van een depressie. De invloed van chronische levensstress op depressieve terugval is minder onderzocht.

Volgens de *scarring* hypothese laat een depressie een litteken achter op psychologisch, sociaal en/of biologisch gebied, waardoor mensen na een depressieve

episode gevoeliger zijn voor terugval. Zo kan de drempel tot terugval steeds lager worden. Of premorbide risicofactoren en levensstress na meerdere episoden kunnen leiden tot de terugkeer van een depressie is niet zeker. In dit proefschrift noemen we een risicofactor die mogelijk is ontstaan na de eerste depressie, een postmorbide risicofactor.

Het onderzoeken van mensen met een hoog aantal voorgaande episoden, zou meer inzicht kunnen geven in veranderingen in bijvoorbeeld cognitieve gevoeligheid en/of stress sensitiviteit.

Inleiding deel 2

Uit diverse meta-analyses blijkt dat behandeling met psychotherapie in de acute fase van een depressie (wanneer iemand aan de criteria voor een depressieve stoornis voldoet), een beschermend effect heeft na herstel van een depressie. Toch is er nog steeds een groot percentage mensen dat terugval ervaart na effectieve acute fase therapie. Daarom wordt er continuatiebehandeling geadviseerd, met name bij mensen met een hoog risico op terugval (o.a. hoog aantal voorgaande episoden, residuele klachten). Continuatiebehandeling bestaat vaak uit dezelfde behandeling die geboden werd tijdens de acute fase. Daarbij komt cognitieve (gedrags)therapie (C(G)T) naar voren als de meer effectieve therapie op de lange termijn, vergeleken met farmacotherapie.

Hiernaast zijn ook psychotherapieën die zich specifiek richten op het voorkomen van depressieve terugval na herstel, effectief gebleken (sequentiële preventieve psychotherapie), zoals Preventieve Cognitieve Therapie (CT) en Mindfulness Based cognitieve gedragstherapie (MBCT). Hierbij lijken Preventieve CT en MBCT met name effectief in het verminderen van terugval bij mensen met een hoog aantal voorgaande episoden, al zijn er eveneens aanwijzingen voor effectieve bescherming op de lange termijn bij mensen met minder voorgaande episoden.

Op dit moment worden veel herstelde mensen nog niet behandeld, door vaak lange wachtlijsten en de beperkingen in de aangeboden zorg. Het bieden van zeer laag intensieve vormen van psychotherapie (bijvoorbeeld minder lang, minder face-to-face

contacten), zou de toegankelijkheid kunnen verhogen. De afgelopen jaren is e-health in opkomst, waarbij bestaande therapieën worden aangeboden met behulp van technologieën als het Internet en mobiele telefonie. Bij therapieën aangeboden via het Internet kunnen mensen op hun eigen moment sessies volgen, en zijn er minder therapeuten nodig. Dit alles zou een kostenreductie met zich mee kunnen brengen en de toegankelijkheid van zorg kunnen verhogen. Het effect van preventieve C(G)T via het Internet, is nog niet onderzocht bij mensen die in herstel zijn van meerdere voorgaande depressieve episoden.

Hoofdbevindingen hoofdstukken in deel 1

Hoofdstuk 2:

In hoofdstuk 2 is onderzocht of een premorbide risicofactor, geoperationaliseerd als het meemaken van het overlijden van een ouder, seksueel misbruik of fysiek misbruik, geassocieerd was met de terugkeer van depressieve symptomen na herstel bij mensen die tenminste twee depressies in het verleden hebben ondergaan. Hieruit bleek dat depressieve symptomen na herstel niet waren geassocieerd met het wel of niet hebben ondergaan van trauma's in de kindertijd.

In het kader van de *vulnerability-stress* hypothese, onderzochten we of trauma's in de kindertijd geassocieerd waren met een verhoogde gevoeligheid voor alledaagse levensstress en daarmee depressieve symptomen na herstel. Alledaagse levensstress was geoperationaliseerd als de frequentie en intensiteit van onafhankelijke stress (stress veroorzaakt onafhankelijk van de persoon zelf, bijvoorbeeld een vriend krijgt een ongeluk), en afhankelijke stress (stress mede-veroorzaakt door de persoon zelf, bijvoorbeeld te veel sociale verplichtingen hebben). Hierbij werd geen bewijs gevonden voor de *vulnerability-stress* hypothese. Het zou kunnen dat mensen met een geschiedenis van voorgaande depressies al gevoeliger zijn voor levensstress, onafhankelijk van nare ervaringen in de kindertijd.

Tot slot werd onderzocht of alledaagse stress geassocieerd was met de terugkeer van depressieve symptomen na herstel. Volgens verwachting bleek de intensiteit van alledaagse stress inderdaad geassocieerd te zijn met depressieve symptomen na

herstel. Tegenstrijdig met de *scarring* hypothese was dit onafhankelijk van het aantal voorgaande episoden. Gezien het hoog aantal voorgaande episoden in de onderzoeksgroep, zou het ook kunnen zijn dat *scarring* al eerder heeft plaatsgevonden. Leren omgaan met alledaagse stress lijkt een mogelijk doel bij terugvalpreventie.

Hoofdstuk 3 en 4:

Internationale behandelrichtlijnen adviseren een langere duur van behandeling aan mensen die lijden aan depressie en een co-morbide chronisch somatische ziekte. Het hebben van een chronisch somatische ziekte wordt gezien als een chronische stressor die het risico op terugval verhoogt. Omdat er geen systematische reviews of meta-analyses zijn uitgevoerd waarin het depressie beloop bij chronisch somatische zieke mensen vergeleken is met niet-chronisch somatisch zieke mensen, beschrijven we in hoofdstuk 3 en 4 of het hebben van een chronisch somatische ziekte geassocieerd is met een hogere kans op depressieve terugval en een lagere kans op herstel.

Een systematische review (hoofdstuk 3), wees uit dat er geen associatie is tussen een hoger risico op depressieve terugval en de aanwezigheid van een chronisch somatische ziekte. In hoofdstuk 4 onderzochten we, aan de hand van een meta-analyse, of de tijd tot herstel verschilde tussen mensen met en zonder een chronische somatische ziekte. De gecombineerde uitkomst van de geïncludeerde studies toonde geen verschil aan tussen beide groepen. Deze bevindingen contrasteren met de huidige aanbevelingen van internationale klinische richtlijnen om mensen met een chronisch somatische ziekte langer door te behandelen. Een specifieke focus op deze groep lijkt daarom vooralsnog niet gerechtvaardigd.

Hoofdstuk 5:

Het hebben van een persoonlijkheidsstoornis is geassocieerd met een hoger risico op terugval en een langere tijd tot herstel. Dit zou verklaard kunnen worden doordat het hebben van een persoonlijkheidsstoornis ook wel wordt gezien als een chronische levensstressor die cognitieve kwetsbaarheid activeert. Omdat nog niet bekend is of het hebben van een persoonlijkheidsstoornis geassocieerd is met cognitieve kwetsbaarheid, richten we ons hierop in hoofdstuk 5.

Cognitieve kwetsbaarheid was geoperationaliseerd als dysfunctionele verwachtingen, cognitieve reactiviteit, extreem denken en rumineren. Er werd geen ondersteuning gevonden voor de *scarring* hypothese, aangezien er geen associatie was tussen het aantal voorgaande episoden en persoonlijkheidsstoornissen. Al kan dit eveneens verklaard worden door het hoog aantal voorgaande episoden dat mensen al hebben meegemaakt. Het hebben van een persoonlijkheidsstoornis was wel geassocieerd met rumineren, dysfunctionele verwachtingen en cognitieve reactiviteit (onafhankelijk van het aantal voorgaande depressieve episoden). Dysfunctionele verwachtingen vertoonde de sterkste associatie met persoonlijkheidsstoornissen. Preventieve CT richt zich onder meer op dysfunctionele verwachtingen, alhoewel we niet weten of de associatie tussen persoonlijkheidsstoornissen en cognitieve kwetsbaarheid daadwerkelijk leidt tot een hoger risico op depressieve terugval.

Hoofdbevindingen hoofdstukken in deel 2

Hoofdstuk 6:

Bekende meta-analyses waarin preventieve behandelingen gericht op het voorkomen van terugval geëvalueerd worden, rapporteren meestal over de effecten van C(G)T. Daarbij is er minder aandacht voor andere therapieën, waaronder interpersoonlijke therapie en Internet-gebaseerde therapieën. In hoofdstuk 6 werden gerandomiseerde trials over psychologische therapieën aangeboden tijdens (gedeeltelijk) herstel geëvalueerd met behulp van een meta-analyse. Hierbij is ook rekening gehouden met de invloed van het aantal voorgaande episoden aangezien in eerder onderzoek Preventieve CT en MBCT alleen effectief leken bij mensen met een hoog aantal episoden.

De resultaten van het huidige onderzoek toonden aan dat preventieve psychologische interventies, waaronder C(G)T, Preventieve CT, interpersoonlijke therapie en MBCT, vergeleken met reguliere zorg en farmacotherapie, effectief waren in het voorkomen van terugval voor een gemiddelde duur van twee jaar. De effectiviteit van preventieve psychologische therapieën, ook MBCT en Preventieve CT, was

onafhankelijk van het aantal voorgaande episoden in tegenstelling tot voorgaand onderzoek.

Hoofdstuk 7, 8 en 9:

Deze drie hoofdstukken richten zich op Mobiele CT. Mobiele CT is een via Internet aangeboden vorm van Preventieve CT met minimale therapeutondersteuning via e-mail, tenminste twee ondersteunende telefonische gesprekken en een geautomatiseerde stemmingsmeter via e-mail of SMS.

In hoofdstuk 7 zijn de details van het onderzoeksdesign van de gerandomiseerde trial naar de (kosten)effectiviteit van Mobiele CT beschreven. Vervolgens zijn in hoofdstuk 8 de korte termijn resultaten van Mobiele CT onderzocht en hoofdstuk 9 beschrijft het gebruik van Mobiele CT.

Uit de eerste resultaten blijkt dat Mobiele CT in aanvulling op reguliere zorg, leidt tot een significante reductie in depressieve symptomen over drie maanden beloop, vergeleken met reguliere zorg, in geheel herstelde mensen die lijden aan recidiverende depressies. Dit effect was onafhankelijk van het aantal voorgaande episoden of het soort reguliere zorg op baseline. Verder bleek het effect van Mobiele CT nog beter wanneer mensen een hoger aantal modules hadden gevolgd.

Uit een evaluatie van het gebruik van Mobiele CT, bleek dat volledige therapietrouw 58.7% was (aantal mensen dat de laatste module heeft afgerond/aantal mensen dat gestart was met eerste module), wat vergelijkbaar is met de 65%-72% gevonden in andere studies over Internet therapieën met therapeutondersteuning. Echter, de gemiddelde tijd die een therapeut nodig had per deelnemer (e-mail en telefoonondersteuning), was slechts 21 minuten. Therapietrouw kan wellicht ook hoog zijn bij minimale ondersteuning. Over het algemeen vonden deelnemers en therapeuten Mobiele CT een acceptabele vorm van behandeling.

Deze korte termijn resultaten wijzen er op dat Mobiele CT toegevoegd aan reguliere zorg, een effectieve en acceptabele vorm van behandeling ter voorkoming van de terugkeer van depressieve symptomen na herstel zou kunnen zijn.

Discussie

Samenvattend kunnen we zeggen dat iedereen die een depressieve episode heeft ondergaan, een risico heeft op terugval. Preventie van terugval is daarom van belang voor iedereen die een depressie heeft meegemaakt, ongeacht het aantal voorgaande episodes.

Echter, hoogstwaarschijnlijk heeft niet iedereen dezelfde soort en vorm van behandeling nodig. Gepersonaliseerde behandeling op basis van de aanwezigheid van risicofactoren voor terugval (aantal voorgaande episoden, instabiele remissie of de aanwezigheid van residuele klachten en mogelijk trauma's in de kindertijd), zou kunnen helpen bij het bieden van de best mogelijke behandeling. Huidige specifieke preventieve behandelingen als Preventieve CT en MBCT zouden ingezet kunnen worden bij mensen met een extreem hoog risico op terugval, terwijl een minder specifieke behandeling, zoals psycho-educatie of zelfs monitoring, ingezet zou kunnen worden bij een relatief minder hoog risico groep op terugval.

Bij het aanbieden en evalueren van preventieve behandelingen zal men in toekomstige studies onderscheid kunnen maken tussen mensen met een extreem hoog risico op terugval en een hoog risico op terugval. Hierbij is het van belang dat er nog meer onderzoek gedaan wordt naar risicofactoren van terugval, zoals bijvoorbeeld het meegemaakt hebben van trauma's in de kindertijd.

E-health, met ondersteuning door therapeuten en mobiele monitoring, als aanvulling op bestaande therapieën kan daarbij het behandelaanbod verbreden.

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Curriculum Vitae

Gemma Kok was born in Gorredijk on August 24th 1982. In September 1999 she started International Business and Languages in Groningen and did this for two years. After that, she started working and thought about what to do next. In September 2002 she began studying Psychology at the University of Groningen. She received her master's degree in Clinical and Developmental Psychology in May 2008, with additional minors in Journalism and Criminology. After combining multiple jobs (e.g. Intelligence testing, working with adolescents with autism), she started her Phd project "Disrupting the rhythm of depression" at the department of Clinical Psychology of the University of Groningen in November 2009. From November 2013 till March 2014 she worked as a lecturer for the department of Clinical Psychology. In addition she worked as a psychologist in a mental health institution from September 2013 till May 2014. In March 2014 she started working as a postdoctoral researcher at the department of Clinical Psychology of the University of Groningen, examining the efficacy of a blended anxiety treatment for children and adolescents.

International publications

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